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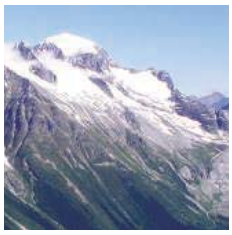


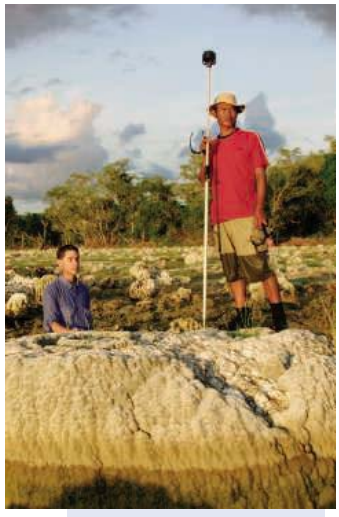
COVER A glacially carved valley in the Mount Waddington region of the southern Coast Mountains, British Columbia, Canada. Repeated glaciation in this region resulted in rapid rates and large magnitudes of erosion, as discussed on page 1668. [Photo: T. A. Ehlers]

Volume 310
9 December 2005
Number 5754

DEPARTMENTS

NEWS OF THE WEEK

NEWS FOCUS



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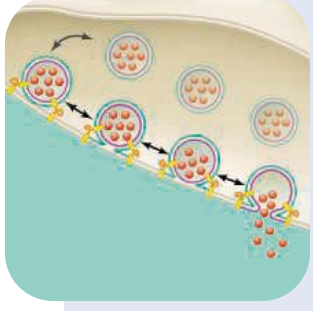

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Why is he so attracted?

Roberto Gradnik
Regional Vice-President, Serono

Italy is currently a key strategic location for Serono, thanks to its competitive costs, excellent research centres and high productivity, comparable to Switzerland or anywhere in Europe. This is why Serono chose to strengthen its Italian presence with a new R&D centre in Rome in 2004. Italian Life Sciences industry is the third largest in Europe, a world market leader in the sector attracting major global companies. The presence of high performing research centres with a proven track record of achievements in Healthcare research and a strong synergy between academia and industry has led to the creation of specialized biotechnology clusters, with excellent perspectives in Oncology and Neurosciences. An array of recent applications in the Biomedical, Bioinformatics, Biomechanics and Nano-biotechnology fields is catching foreign investors' attention.
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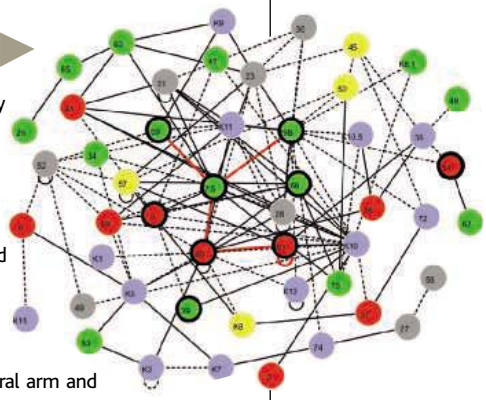
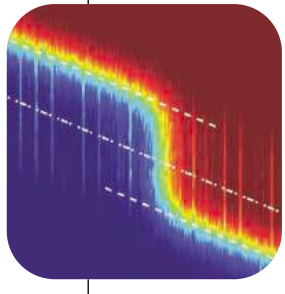


TECHNICAL COMMENT ABSTRACTS



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Protein kinases validated with FA platforms	201	80
Cell lines for pathway analysis	29	0
Protein kinases addressed by RNAi platform	ALL	<100

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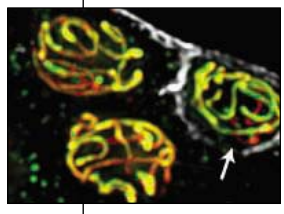
*All data pulled from competitor's web site as of 11/8/05.

Reports continued



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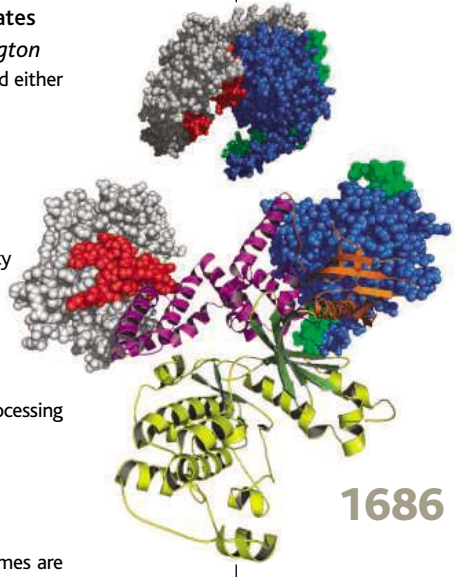

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“My research focuses on identifying functional and molecular differences between (…)”

(…) individual dopaminergic midbrain neurons, involved in disease patterns such as drug addiction, Schizophrenia and Parkinson’s disease. Single-cell gene expression analysis techniques including the Leica Microdissection system are crucial for our research.”

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Autistic kids have less activity in brain region associated with empathy.

Love Is an Open Wound
When married couples argue, their physical injuries take longer to heal.

Bees Recognize Human Faces
Complex ability may not require complex brain.

More scientists needed?

science's next wave www.nextwave.org Career Resources for Young Scientists

US: What's Wrong with American Science? *B. Benderly*
A new National Academies report calls for more scientists for the United States to remain competitive.

MiSciNet: Piecing Together the Past *R. Arnette*
Physical anthropologist Rachel Watkins examines human skeletons in search of cultural clues.

Europe: Jump First, Consider the Risks Later *E. Pain*
An Italian entrepreneur, now a Silicon Valley executive, describes how he ran with a good idea.

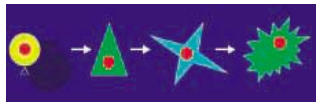
Germany: Independence for Young Scientists *S. Lehmann*
The German Research Foundation's Emmy Nother Programme strives to give researchers scientific independence at a relatively young age.

US: Making the Most of Career Fairs *G. Fowler*
Before you attend a career fair, ask yourself what kind of scientific career you are looking for.

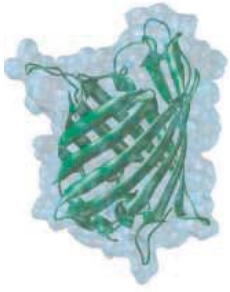
science's sage ke www.sageke.org Science of Aging Knowledge Environment

Perspective: Living Longer and Paying the Price? *J. Q. Trojanowski, M. K. Jedrziewski, D. A. Asch*
Conference featured discussion of health care costs and longevity in America.

News Focus: Tapping into Renewal *M. Leslie*
Compound that boosts cell division slows Huntington's disease in mice.



Growing out of Huntington's disease?



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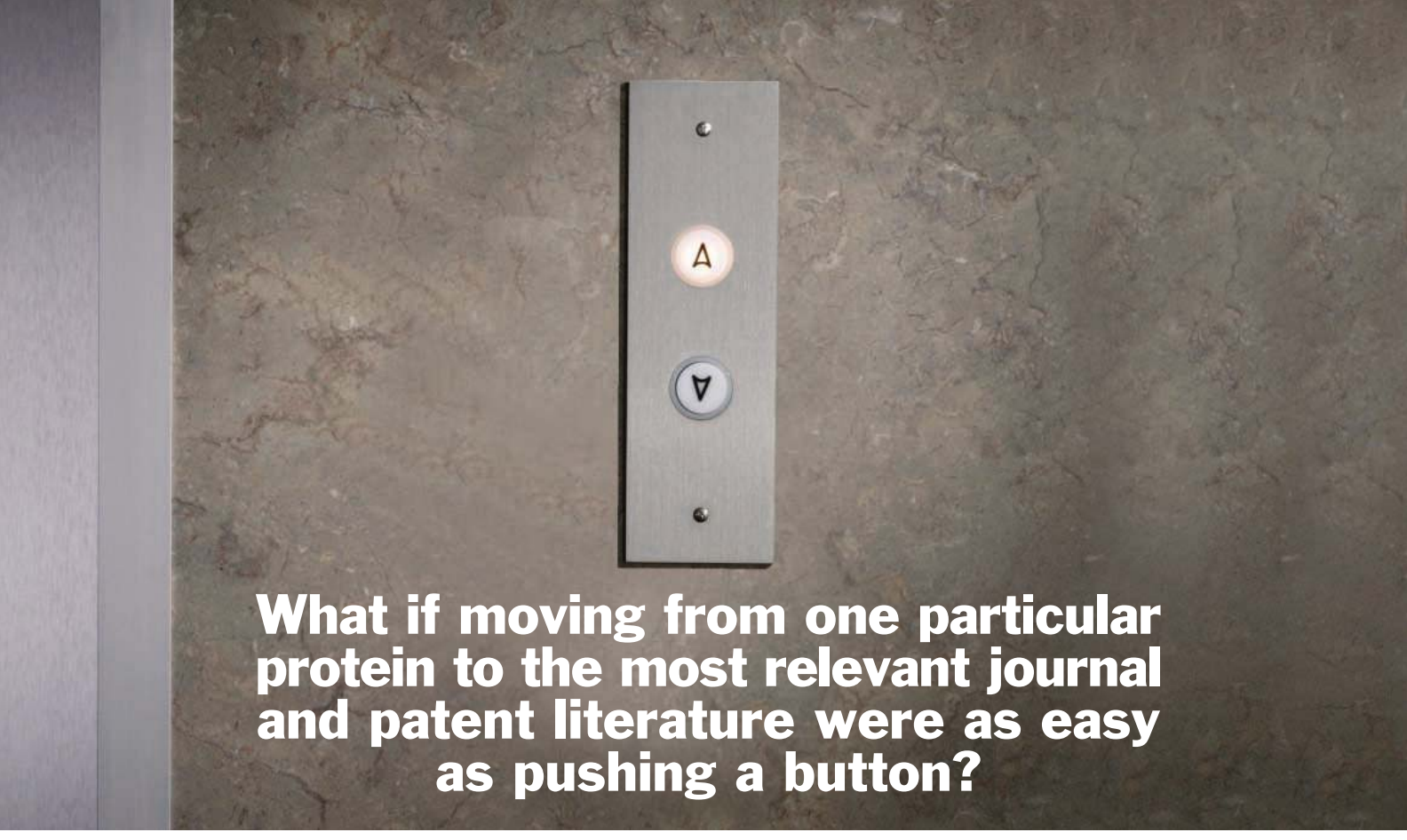

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Restoring the Forests

Deforestation in the tropics has had seriously adverse consequences for biodiversity, ecosystem services, and the human inhabitants of the tropical forest. In recent years, projects have been set in motion to restore degraded forest lands in some countries. **Lamb *et al.*** (p. 1628) review the range of approaches to restoration and assess the extent to which these approaches might be successful in achieving their aims, particularly with respect to human well-being.

Rapid Glacial Erosion

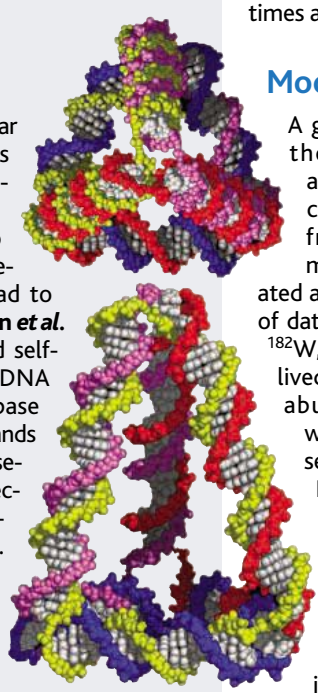
Determining the relative importance of incision by rivers and glaciers in the creation of alpine valleys is often hampered by difficulties in quantifying rates of glacial erosion. **Shuster *et al.*** (p. 1668; see the cover) assessed the timing and rate of glacial erosion by $^{4}He/^{3}He$ thermochronometry. Using an example from the Coast Mountains of British Columbia, Canada, they determined erosion rates both before and during alpine glaciation. The Klinaklini Valley deepened rapidly by 2 kilometers or more around 1.8 million years ago when it became glaciated, at least six times as fast as during its preglacial state.

Superconducting Qubit Interferometry

Mach-Zehnder interferometry is a powerful technique to probe quantum optical effects. Such interferometers contain two beam splitters. The first sends two beams of photons along separate paths. The acquired path or phase difference the two beams may acquire creates interference fringes after the second beam splitter recombines the two beams. **Oliver *et al.*** (p. 1653, published online 10 November) show that a two-level superconducting qubit can also be made to exhibit similar interference fringes. In this case, the anticrossing between the ground and excited states acts as the beam splitter, and the energy level splitting between them corresponds to the optical path difference. Multiple photon transitions (up to 20) can be induced, thus illustrating a potentially useful route for the manipulation of superconducting qubits in quantum computing schemes.

DNA Twisted into Tetrahedra

One strategy for building molecular nanostructures in three dimensions is to exploit the connectivity afforded by nucleic acid structures. In many cases, the steps needed to select particular base pairing to create structures such as cubes lead to long, multistep syntheses. **Goodman *et al.*** (p. 1661) have developed a rapid self-assembly process that creates DNA tetrahedra that have 10 to 30 base pairs on each edge. Four single strands that contain the complementary sequences for six edges anneal in seconds in 95% yield, and single diastereomeric products are formed. The authors also present atomic force microscopy studies of the compression of a single DNA tetrahedron.

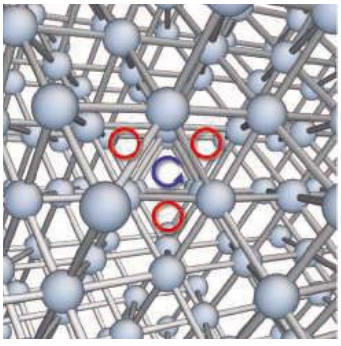


Moon Magma

A giant impact into the early Earth is thought to have ejected a huge amount of debris into orbit that coalesced to form the Moon. Heat from the impact also apparently melted much of the Moon and created a huge ocean of magma. One means of dating these processes is by detecting ^{182}W, the daughter product of a short-lived isotope, ^{182}Hf. Differences in the abundances of ^{182}W are produced when magma, rocks, and crystals separate while ^{182}Hf is still present. **Kliene *et al.*** (p. 1671; published online 24 November) report accurate measurements of tungsten isotopes by analyzing metals returned in Apollo samples (metals provide the most accurate measure). The data imply that the giant impact occurred about 30 million years after the formation of the solar system and that the magma ocean had solidified by about 50 million years.

Going Softer

Whether added deliberately or by accident, impurities or solutes have long been used to strengthen metals. A more recent discovery was that impurities can soften some metals, but the underlying reasons have not been fully understood. Using simulations, **Trinkle and Woodward** (p. 1665; see the Perspective by **Chrzan**) show that for molybdenum, certain transition metal solutes can influence the energy barriers for dislocation motion, and in some cases, these changes lead to a softening of the metal. By reducing the strength, and thus the tendency to fracture abruptly, these modified metals may find expanded use in structural components.



Protein Interaction in the Gaseous Phase

The identification of transient or readily reversible interactions between proteins is a difficult problem that has been addressed with a variety of methods. **Ruotolo *et al.*** (p. 1658; published online 17 November) have now applied mass spectrometry to the problem in order to exploit its advantages of sensitivity and speed. They show that the *trp* RNA-binding attenuator protein (TRAP) maintains its 11-membered ringlike structure in the gas phase and that binding of RNA and tryptophan influences the shape and stability of the ring in a fashion consistent with its known behavior in aqueous solution.

The Liver and the Control of Glucose Metabolism

The protein kinase and tumor suppressor LKB1 is a potential activator of the adenosine monophosphate–activated protein kinase (AMPK), a kinase that senses cellular energy levels by binding the metabolite AMP. **Shaw *et al.*** (p. 1642; published online 24 November)

CONTINUED ON PAGE 1583

CREDITS (TOP TO BOTTOM): GOODMAN *ET AL.*; TRINKLE AND WOODWARD

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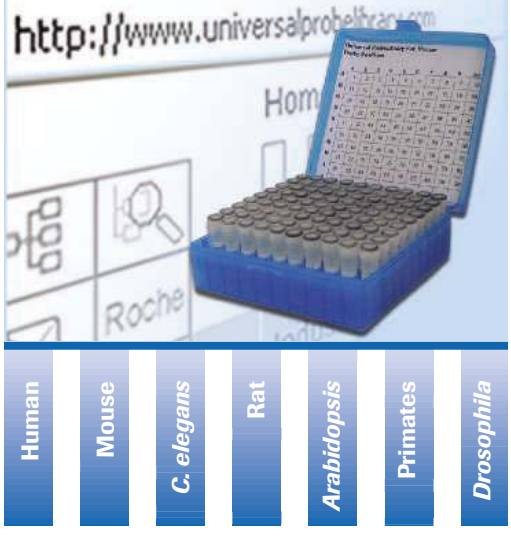

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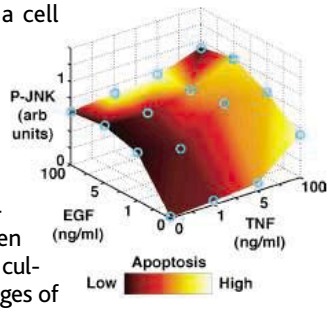
engineered mice so that LKB1 expression could be acutely blocked only in the liver; they found that its expression plays a critical role in the control of metabolism in the liver and in glucose homeostasis. In the absence of LKB1, AMPK was almost completely inactive. Animals lacking LKB1 in the liver showed hyperglycemia and increased expression of genes encoding enzymes of gluconeogenesis and lipogenesis.

Predicting Responses on the Death Pathway



Multiple signaling pathways can influence whether a cell commits to the cell death program known as apoptosis. For many years, it has been possible to categorize signals as contributing to the "gas" or to the "brakes." However, predicting the biological outcome of multiple signals that apply some gas here, and a stomp on the brakes there, has remained a challenge. **Janes *et al.*** (p. 1646) applied a systems-level approach to this problem and created a model to analyze coupling between almost 8000 measurements of signaling parameters in cultured cells with about 1500 measures of the various stages of apoptosis in cells treated with various combinations of cytokines. The model allows the cellular apoptotic response to be correctly predicted under a variety of conditions.

Land-Use Effects on Climate

Climate models are still only rather crude representations of real climate systems, and one class of important feedbacks not adequately realized in them is that of land processes. **Fedemma *et al.*** (p. 1674; see the Perspective by **Pielke**) investigate the role of biogeophysical land processes, which directly affect the absorption and distribution of energy at the Earth's surface, by integrating them into a global climate model. Increases in atmospheric CO_2 concentrations during the next century and associated greenhouse gas–induced warming led to significant regional impacts directly associated with land cover, mostly in mid-latitude and tropical areas. However, global average temperature was not affected much by land cover change because regional variations that led to more or less warming tended to cancel out.

Lipids and Neurotoxins

The venom of certain snakes includes neurotoxins capable of paralyzing their victims. Upon intoxication, snake presynaptic phospholipase A2 neurotoxins (SPANs) cause motor nerve terminals in the neuromuscular junction to enlarge and induce exocytosis of neurotransmitters from synaptic vesicles. **Rigoni *et al.*** (p. 1678; see the Perspective by **Zimmerberg and Chernomordik**) now find that a mixture of lysophospholipids and fatty acids, which are released by SPANs acting on phospholipids, closely mimics all of the biological effects of SPANs. Thus, at the presynaptic membrane, lysophospholipids and fatty acids help to generate a membrane conformation that promotes vesicle exocytosis and also inhibits synaptic vesicle retrieval.

Ambiguity Averse

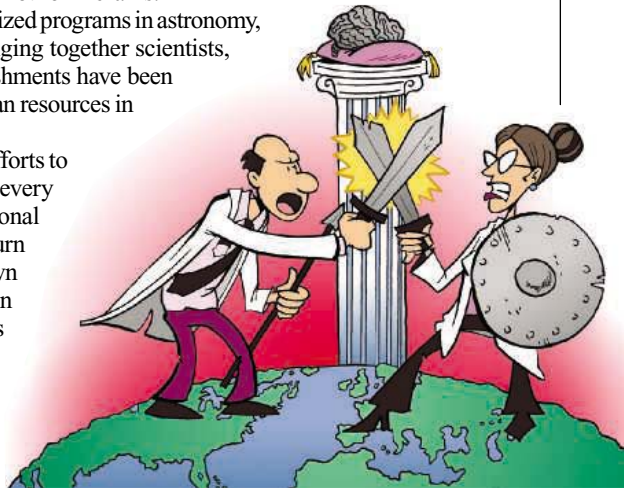
In a 2002 news briefing, U.S. Secretary of Defense Donald Rumsfeld famously distinguished between known knowns, known unknowns, and unknown unknowns. The last group remains difficult to discuss, but neuroscientists and economists have joined forces to examine the distinctions between the first two. **Hsu *et al.*** (p. 1680; see the Perspective by **Rustichini**) challenged subjects to choose between risky and ambiguous payoffs, where the former type of choice contains outcomes with known probabilities and the latter type features the same outcomes but with unknown probabilities. Even under conditions where the expected payoffs are equal, normal humans prefer risk over ambiguity, and brain-imaging results suggest that the amygdala and orbitofrontal cortex (OFC), which both become more active with ambiguity, modulate a third area of the brain, the striatum. Notably, patients bearing lesions in the OFC did not exhibit an aversion to ambiguity.

CREDIT: JANES *ET AL.*

Battle for the Brains?

Scientific talent is always attracted to the heights of excellence, and those can often reside in world locales other than where the talent burgeoned in the first place. The result has been a global mixing of minds that has nurtured many splendid contributions to human knowledge based on expertise from all corners of the world. So it is disturbing to hear politicians, economists, and academicians frequently bemoan a country's loss of young talent, describing a "brain drain" that could damage national self-interest. This is an unfortunate description, leaving the impression that a society should not encourage its people to learn and work in countries that offer an opportunity for further intellectual and social growth on many levels. However, this is exactly what societies should do if we are to be successful in solving the world's frightening problems such as climate change, sustainable energy supplies, water management, and epidemic infectious diseases. What we need is the most talented scientific minds, whatever their origins, for a battle of—not for—brains.

The past few decades have seen the development of internationally organized programs in astronomy, climate, biodiversity and global ecology, and the health sciences. By bringing together scientists, economists, and politicians from different countries, significant accomplishments have been made that would have been impossible without some concentration of human resources in particular places. That can't happen without some drainage in others.



The participation of its best and brightest talents in these international efforts to solve humankind's common problems constitutes a future guarantee for every nation, which then becomes part of the self-organizing network of international cooperation. And the contribution yields benefits when their nationals return home (either temporarily or permanently) to strengthen their country's own innovative capacity, economy, and social capital. When politicians complain about losses from a brain drain, it conjures a view of scientific talent as some kind of national heritage or even property. They describe a "loss" of intellectual talent as a threat to competitiveness and say that the depletion of intellectual human resources must be reversed. But these human resources are individuals who should be able to decide for themselves where to settle, to learn, and to work, either for a period or permanently. There are many different and often personal reasons for scientific emigration; no single attribute of a particular destination explains why it occurs.

According to the German Research Council, about two-thirds of all German postdoctoral fellows who go abroad (including more than 70% in the natural sciences, biosciences, and engineering) spend their training period in the United States, as compared to some 15% in member states of the European Union. Of the approximately 15 to 20% that remain abroad, only 40% do so in the United States (and about the same proportion in the European Union). Decades of experience have convinced me that the 85% of the German scientists who return from the United States bring improved expertise, knowledge of other languages and cultures, and many excellent connections with scholars from all over the world. I cannot think of a better way in which to link my country with leading developments in science, humanities, and technology in the rest of the world.

Science as a global social enterprise needs continuous stimulation through diversity of cultural traditions, languages and literatures, styles of education, gender, and giftedness. The United States alone receives many thousands of young foreigners every year in its higher educational system, which is often perceived as a one-way street. The United States should encourage its own rising talents to go abroad, expose themselves to foreign cultural influences and languages, and even risk being more permanently attached to those other societies. Although some of the highest ground in certain disciplines may be found at home, that won't be true for all; some U.S. scientists who have ventured abroad have become their own foci of attention. At the Max Planck Society, more than one-quarter of the 278 scientific directors are foreigners, many of whom are American.

So let's worry less about brain drain and instead strengthen scientific ties by encouraging drainage in both directions. "Mind swapping" across the ocean unites intellectual forces for the common pursuit of knowledge, and that, after all, is the better part of the "pursuit of happiness" for scientists. Let's focus on gathering together to confront the troubling challenges that await scientists who now serve a global society.

Hubert S. Markl

Hubert S. Markl is a retired professor of Biology, University of Konstanz, Konstanz, Germany, and past president of the Max Planck Society, Munich, Germany.

10.1126/science.1122664

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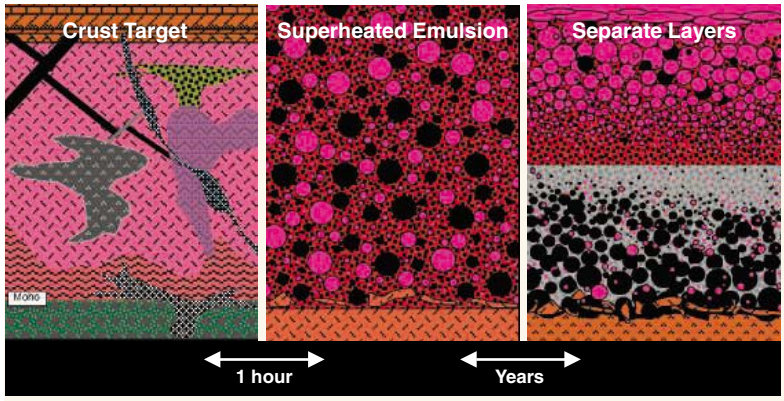
edited by Gilbert Chin



The early stages of emulsification and separation (norite, black blobs; granophyre, red blobs).

GEOCHEMISTRY

Emulsifying the Crust

Not quite 2 billion years ago, a large asteroid stuck itself into what is now eastern central Ontario, forming the Sudbury impact crater. The energy of the impact melted a large amount of the continental crust, producing a thick melt sheet that was initially about 1700°C, well above the liquidus for norite (~56% silica) and for granophyre (~70% silica).

Zieg and Marsh describe the subsequent evolution and cooling of this molten body as a natural experiment that can be compared to the formation of magma bodies in igneous intrusions such as those underlying volcanoes. The superheated Sudbury melt sheet began as an emulsion containing droplets of silica-rich and silica-poor magma; the less dense, silica-rich drops separated within months and coalesced into an upper melt sheet. Vigorous convection in both sheets occurred until they cooled to the liquidus, at which time crystals began to form and convection ceased. The combined melt layers solidified from the top and bottom. Aside from the initial separation of the two liquids, the solidified sheet shows little compositional gradations. Early formed crystals are dispersed throughout, and layers are not apparent. These textures contrast with those of many igneous magma bodies, suggesting that the latter may not have originated as large hot chambers at an instant in time. — BH

Geol. Soc. Am. Bull. **177**, 1427 (2005).

BIOCHEMISTRY

Ribosomal Logic

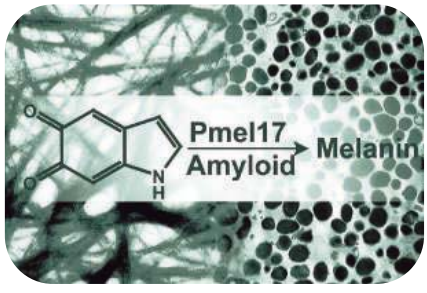
The recently acquired appreciation of metabolic and regulatory pathways as an immensely complicated wiring diagram has been accompanied by attempts to reroute and redefine these circuits by adding and subtracting switches and connectors. One challenge, of course, is to maintain cell viability while tinkering with macromolecular components whose interactions may not yet be completely specified. Rackham and Chin have developed an orthogonal approach—building a parallel metabolism within a cell—by selecting for modified Shine-Dalgarno sequences that bind to correspondingly modified 16*S* ribosomal RNAs (rRNAs) and that no longer bind to wild-type 16*S* rRNAs. Amazingly, these orthogonal 16*S* rRNAs still assemble into competent ribosomes, and placing the cognate Shine-Dalgarno sequence in front of a reporter gene results in faithful translation of an active enzyme independently of the endogenous protein synthesis machinery. Introducing several pairs of orthogonal messenger RNAs and rRNAs allows for the construction of AND and OR gates within otherwise unperturbed *Escherichia coli*. — GJC

J. Am. Chem. Soc. 10.1021/ja055338d (2005); *Nat. Chem. Biol.* **1**, 159 (2005).

CELL BIOLOGY

A Good Amyloid

Amyloids are an insoluble fibrous form of protein aggregates and are generally associated with a variety of neurodegenerative disease states. Fowler *et al.* find that in melanocytes, intracellular amyloid is not a pathological aberration but instead plays a productive role in melanin formation. Melanin is a tyrosine-based polymer that protects organisms from some toxins and ultraviolet radiation. In mammalian melanocytes, melanin is produced within membrane-bound organelles known as melanosomes, with the aid of the protein Pmel17. During this process, it appears that Pmel17 adopts an amyloid-like structure that provides a template for the assembly of melanin precursors, and recombinant Pmel17 amyloid was observed to accelerate melanin production in vitro. Within the cell, the Pmel17-containing amyloid could also serve to sequester highly reactive intermediates in melanin biosynthesis. — SMH



Pmel17 fibers (left), melanosomes (right), and the melanin-producing reaction (center).

PLoS Biol. **4**, e6 (2006).

SURFACE SCIENCE

Subsurface Manipulation

The movement of hydrogen into and out of the bulk regions of metals is important in hydrogen storage, metal embrittlement, and fuel cell reactions. Sykes *et al.* used voltage pulses delivered via a scanning tunneling microscope tip to manipulate subsurface hydrogen atoms. They applied bias pulses of >0.5 V to a Pd(111) surface held at 4 K that had had hydrogen removed from its near-surface region by oxygen treatment. These bias pulses were able to excite residual hydrogen atoms in the bulk (which has a population of one H atom per 2000 Pd atoms) and allowed these atoms to move into more energetically favorable subsurface sites. The subsurface hydride depleted the surface Pd atoms of charge and caused an outward surface relaxation of Pd atoms of 0.1 to 0.6 Å. Surface hydrogen also tended to move away from these regions to leave behind ordered arrays of overlayer vacancies. — PDS

Proc. Natl. Acad. Sci. U.S.A. 10.1073/pnas.0506657102 (2005).

CONTINUED ON PAGE 1589

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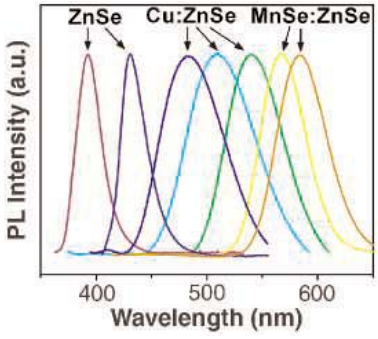
CHEMISTRY

All in the Dope

Cadmium selenide nanoparticles are used in light-emitting diodes, lasers, and sensors and for biological labeling. However, the toxicity of cadmium is a major concern. Zinc chalcogenides, such as ZnSe, doped with transition metal ions may offer as much flexibility and dynamic range as CdSe, but it has been difficult to dope particles uniformly. Recent success in separating the nucleation and growth phases in making high-quality nanoparticles prompted Pradhan *et al.* to consider whether efficient and controlled doping could be introduced. For growth-stage doping, seed ZnSe particles were quenched, and copper was then added as a dopant. Overgrowth with additional ZnSe shifted the photoluminescence (PL) toward the red wavelengths. For the nucleation strategy, Mn was added to shift the PL even further toward the red. The nanoparticle syntheses were performed as one-pot reactions so control of the doping relative to the nucleation or growth could be achieved by varying the reactivity of the precursors and the temperature. — MSL

J. Am. Chem. Soc. 10.1021/ja055557z (2005).



Spectral shifts with dopants.

CREDITS: PRADHAN *ET AL., J. AM. CHEM. SOC.* 10.1021/JA055557Z (2005)

ECOLOGY

Fisheries Failures

Some collapsed fisheries fail to recover even when harvesting has stopped for more than a decade. Fishing usually targets the largest, oldest, and fastest-growing individuals and hence favors the survival of smaller, younger, and slower-growing fish. Walsh *et al.* have chosen the Atlantic silverside, a commercially exploited fish with an annual life cycle, for harvesting experiments under a variety of regimens. They found that selecting out the largest individuals affected multiple traits in subsequent generations, with significant reductions in vertebral number, egg size and subsequent viability; rates of growth and growth efficiency; and foraging and fecundity. It is still not clear why some fish stocks fail to recover and others are more resilient, although duration and intensity of exploitation may be a factor. The authors are continuing to monitor rates of recovery of the experimental silverside populations. — CA

Ecol. Lett. **8**, 10.1111/j.1461-0248.2005.00858.x (2005).

HIGHLIGHTED IN *SCIENCE*'S SIGNAL TRANSDUCTION KNOWLEDGE ENVIRONMENT

Science's STKE www.stke.org

Remember That Gradient?

During early development, morphogen gradients instruct the differentiation of distinct cell types in proper spatial order. Exposure of cells to a specific concentration of morphogen can specify cell fate, but the exposure does not need to last for the several hours needed to complete execution of the gene expression program that drives the cell's response. Jullien and Gurdon explored how cells remember a brief exposure to morphogen by studying responses of *Xenopus* embryo cells to activin. Exposure for 10 min resulted in changes in gene expression several hours later. This response appeared to require continuous receptor signaling, because it could be inhibited at later stages by a pharmacological inhibitor of kinase activity of the activin receptor. Continued signaling also appeared to require receptor internalization, because a dominant-negative form of dynamin that prevents internalization of receptors from the plasma membrane inhibited activin-dependent gene expression when injected into embryonic cells. Expression of mutant Rab proteins that increase trafficking of membrane proteins through the lysosomal pathway (and thus increase the rate at which they are degraded) did not affect the memory of the activin signal, and the authors concluded that the signaling receptors have not yet entered the degradation pathway. Rather, it seems that the persistence of vesicles as they move from the plasma membrane to the lysosome accounts for the signal, and the authors propose that receptors activated by brief exposure to activin provide a prolonged signal. — LBR

enes Dev. **19**, 2682 (2005).

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Information for Contributors

See pages 135 and 136 of the 7 January 2005 issue or access www.sciencemag.org/feature/contribinfo/home.shtml

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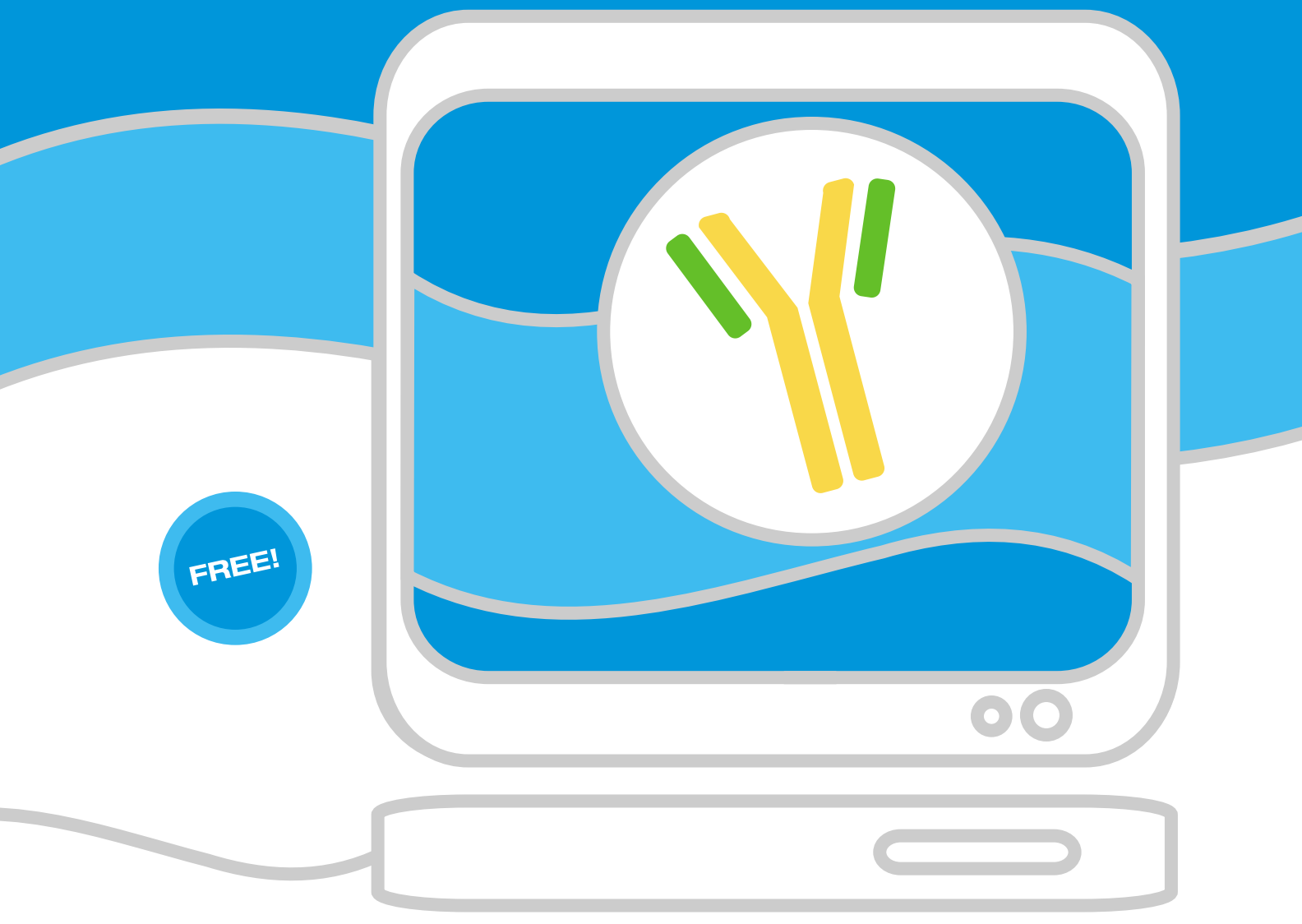

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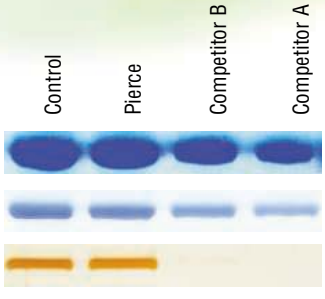

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Protein recovery after sample processing with commercially available desalting resins in a micro-spin device. Samples of bovine serum albumin (BSA) or ubiquitin at a variety of concentrations were desalted with Pierce high-performance desalting resin (Product # 89877) or the leading competitors' resins in empty Zeba™ Micro Spin Columns from Pierce. In all cases, sample volume was 10 µl plus a 3 µl buffer stacker placed over the sample.

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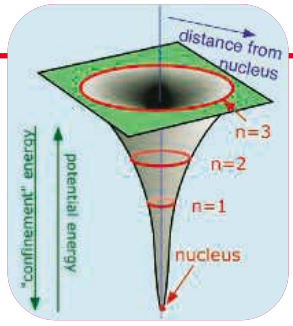


WEB TEXT

Clickable Chemistry

Cracking this virtual chemistry text might spark an interest in electrochemistry or help readers soak up the properties of water. Retired chemistry professor Stephen Lower of Simon Fraser University in Burnaby, Canada, wrote the virtual primer in part to offer an alternative to "commercial textbooks which in my view possess far too much sameness and shallowness." Eleven chapters cover fundamentals such as measurement, chemical equilibrium, and bonding. A new section tackles atomic structure, explaining concepts such as why electrons don't plunge into the positively charged nucleus (above). For students who want more, the book's tutorials dig deeper into particular topics.

www.chem1.com/acad/webtext/virtualtextbook.html

COMMUNITY SITE

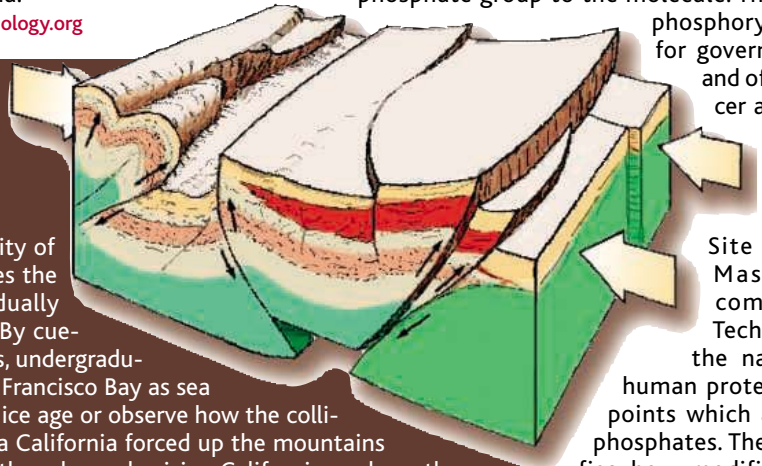
Social Studies

Social psychologists investigate topics as varied as the techniques of propaganda, group dynamics, and facial expressions. A gathering place for students and researchers in this diverse field is the Social Psychology Network, managed by Scott Plous of Wesleyan University in Middletown, Connecticut. For users who need a tutorial on persuasion and influence or want to locate an online experiment their classes can participate in, the network's archive holds links to more than 12,000 resources on other Web sites. Separate discussion forums let students and professionals sound off. If you'd like to team up with a researcher who works on, say, conflict resolution and personality, check the directory with profiles of 1100 or so social psychologists. There are also links to relevant stories in the media.

www.socialpsychology.org

EDUCATION

Making the Earth Move



This collection from the University of California, Santa Barbara, presses the fast-forward button on gradually unfolding geological processes. By cueing the more than 20 animations, undergraduates can follow the filling of San Francisco Bay as sea levels rose at the end of the last ice age or observe how the collision between California and Baja California forced up the mountains north of Los Angeles (above). Although emphasizing California geology, the site also includes examples from other parts of the globe, such as a sequence that tracks the formation of the South Atlantic Ocean as Africa and South America pushed apart. Educational users can download the animations for free.

emvc.geol.ucsb.edu/downloads.php

IMAGES

Truly Heaven Sent?

The man who bought this glossy, 19-kilogram orb (below) was certain he'd nabbed a genuine space rock—and for only $10. To his dismay, lunar geochemist Randy Korotev of Washington University in St. Louis, Missouri, recognized that it was not a meteorite but a coal ball, a compacted glob of peat. To avoid making the same mistake, visit Korotev's A Photo Gallery of Meteorwrongs, which showcases more than 100 objects misidentified as meteorites. Korotev and colleagues have either examined the finds or studied photographs of them. Captions explain why each specimen probably isn't a meteorite and indicate its likely identity. For instance, the coal ball's nearly spherical shape is a giveaway, as is the presence of calcite, a mineral meteorites lack. The site also illustrates criteria for recognizing space stones, including the presence of a fusion crust, a glassy coating formed when the outer layer melts and then solidifies during descent.

epsc.wustl.edu/admin/resources/meteorites/meteorwrongs/meteorwrongs.htm

DATABASES

Phospho Finder

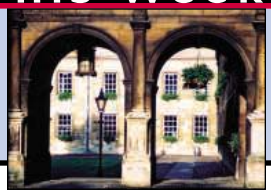
When cells need to switch a protein on or off, they often affix a phosphate group to the molecule. This process, known as phosphorylation, is important for governing protein activity and often goes awry in cancer and other diseases. To find out where phosphates glom onto a particular protein, check out PhosphoSite from the Beverly, Massachusetts–based company Cell Signaling Technology. Users enter the name of a mouse or human protein, and the site pinpoints which amino acids pick up phosphates. The output often specifies how modifications at different positions alter the protein's function. Data gleaned from the literature are free, but access to the company's experimental findings may require a subscription.

www.phosphosite.org

Send site suggestions to netwatch@aaas.org. Archive: www.sciencemag.org/netwatch

CREDITS (TOP TO BOTTOM): STEPHEN LOWER; RANDY KOROTEV; TANYA ATWATER/UNIVERSITY OF CALIFORNIA, SANTA BARBARA

This Week



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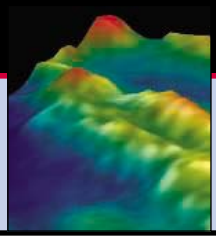
Cambridge's patent debate



1598
Europe's Titanic missions

SPACE SCIENCE

NASA Starts Squeezing to Fit Missions Into Tight Budget

While the public is focused on NASA's attempts to prepare the still-grounded space shuttles for a mid-2006 launch, the agency's science program is also in the midst of a painful, though less visible, overhaul. In the past few weeks, NASA managers have decided to delay by 2 years the flight of a new space telescope and halted work on an asteroid mission that is nearly on the launch pad, and they are reconsidering plans to revive a mission to Jupiter's moon Europa. "We've got to get everything under control," says Mary Cleave, NASA's new science chief. "We're overcommitted."

Meanwhile, another part of the agency has begun to cancel a slew of life sciences experiments slated for the international space station, despite a National Academies' report released 28 November that criticized NASA's scaling back of research on the orbiting base. "We're refocusing on near-term needs," explains NASA exploration chief Scott Horowitz. The agency intends to slice in half the roughly $1 billion it spends annually on biological and physical sciences research; the other half will be devoted primarily to ensuring the health of astronauts on lunar and Mars missions, which are the centerpiece of President George W. Bush's plan to return humans to the moon and send them on to Mars. The vast majority of exploration funding will be devoted to building new launchers.

NASA managers laid out their plans and problems at a meeting last week of the newly reconstituted NASA Advisory Council, which gathered in Washington, D.C., for the first time since Administrator Michael Griffin took over the agency this spring. NASA's $5.5 billion science budget grew slightly in 2006 and is likely to win a modest increase in the president's upcoming 2007 request to Congress. But that budget can't keep up with rapidly rising costs for science projects such as the James Webb Space Telescope (JWST), the successor to the Hubble Space Telescope.

A technical and scientific review this fall managed to reduce significantly the $1 billion overrun on the $3.5 billion JWST (*Science*, 2 September, p. 1472). Still, a host of problems, including delays in winning U.S. government approval for a European launch and difficulties in instrument design, forced Cleave last month to postpone the launch date from 2014 to 2016. That delay, in turn, ate up the savings from the fall review. "The cost is still $4.5 billion," says JWST project scientist Eric Smith. The additional funding, Cleave told *Science*, must be found within the agency's already-strained astronomy and astrophysics budget.

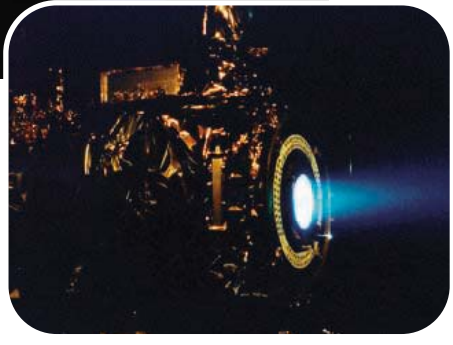
The fate of a proposed mission to Europa—already canceled twice because of its high cost—is now again in question. Planetary scientists are eager to return to the moon, and a 2002 National Academies' panel rated it the top planetary priority in its decadal plan. Griffin promised shortly after taking the job last spring that he would press for a conventional mission following cancellation of plans for a nuclear-powered spacecraft that would orbit Jupiter's moons. Cleave told the council, however, that budget pressures might yet again delay the probe.

"We wouldn't necessarily say our next outer planet mission is to Europa," Cleave later told *Science*. Instead, she would prefer to hold a competition to see if scientific interest in the mission has shifted since the decadal report. But given the stresses on the existing science budget, other agency officials and outside scientists say privately that it would be difficult to start an expensive new outer planets mission before 2008.

Even NASA projects nearing their launch dates are getting extra scrutiny. Cleave recently halted all work on Dawn, a $373 million spacecraft set to blast off next summer on a mission to examine two large bodies in the asteroid belt. Technical and managerial troubles and a resulting spike in costs attracted the attention of NASA headquarters' managers this fall, and Cleave ordered the Jet Propulsion Laboratory in Pasadena, California, to cease work pending a detailed independent assessment to be completed next month. Ironically, the project is part of the Discovery program that is intended to launch missions relatively cheaply and quickly.

Probes already aloft also face a squeeze. On 6 December, NASA shut down the Upper Atmospheric Research Satellite launched in 1991 that measures ozone, winds, and temperature. In October, it abandoned the Earth Radiation Budget satellite after more than 2 decades in orbit. NASA and outside reviewers are considering the fate of a host of planetary and astrophysics spacecraft as well. In addition, a 6-month delay in launching the Earth probes CloudSat and CALIPSO will cost at least $15 million. Cleave has also ordered cuts to the future Mars program.

Lunar research, however, is almost ▶



Dawn breaks? NASA has stopped work on Dawn and its ion-propulsion system to reach two asteroids.

CREDITS: WILLIAM K. HARTMANN, COURTESY OF UNIVERSITY OF CALIFORNIA, LOS ANGELES; (INSET) NASA/JPL

1602
A year after the tsunami

1606
Preventing malaria

1610
Fusion with less brute force?

certain to receive more funding in coming years, given the White House focus on the moon. Horowitz's office will launch a lunar orbiter in 2008 to reconnoiter for possible landing sites, and Cleave hopes to include a bevy of scientific instruments on the flight. She told the council that supporting any more lunar research, however, would leave less for other areas of science.

Although Cleave is an ecologist by training, she has no oversight of NASA's biological and physical sciences. That portfolio belongs to Horowitz, who is drastically reducing funding for a host of experiments designed for the space station. He's already canceled at least half of NASA's current life sciences grants and contracts. Much of the research planned for the station has little connection with Bush's plan to return astronauts to the moon and continue to Mars, Horowitz told *Science*.

That view is at odds with a new report from the National Academies, which warns that abandoning fundamental biological and physical research "is likely to limit or impede" research into the impact of the space environment on astronauts. The panel notes that "once lost, neither the necessary research infrastructures nor the necessary communities of scientific investigators can survive or be easily replaced." The panel argues that NASA needs a detailed plan to use the station for a host of research endeavors, including studies on the effects of radiation on biological systems, loss of bone and muscle mass during space flight, fire safety, and flow and heat-transfer issues. Several Democratic lawmakers are critical of the cuts in life sciences research, but staffers and lobbyists say that their voices are unlikely to rescue the projects.

Stretched thin. NASA's Mary Cleave says space science is "overcommitted."

Even if Horowitz were to reverse his decision, NASA's plans to halt shuttle flights by 2010 would make it difficult to carry out some research on the space station. William Gerstenmaier, head of NASA's space flight efforts, told the agency's advisory council that the shuttle is needed to return experiments and materials to Earth. Without those flights, he says, "you would have to do more in situ research." That research, in turn, would require more complex equipment and crew time.

NASA needs an additional $1.4 billion to redesign space station parts and buy spares so that the station can keep operating without the shuttle, Gerstenmaier added. That money is part of an estimated $6 billion in additional funding for space flight that is not yet included in NASA's future budgets. On top of that long-term fiscal crisis, the agency expects to receive from Congress less than half of the $760 million in damages its facilities suffered from Hurricane Katrina. Congress may also impose an across-the-board cut to all agency budgets to cover hurricane costs, although that didn't stop it from inserting nearly $300 million in pork-barrel projects into NASA's $16.46 billion budget. Such external pressures spell additional trouble for a science effort already suffering from its own excesses. **–ANDREW LAWLER**

STEM CELLS

Landmark Paper Has an Image Problem

New questions about scientific validity are dogging South Korean cloning researcher Woo-Suk Hwang and his colleagues. On 4 December, Hwang notified *Science* editors that a figure in online material that accompanies his group's heralded 2005 paper on the derivation of stem cells from cloned human embryos contained duplicate images. The problem follows close on the heels of Hwang's admission that, despite his previous denials, two members of his lab had donated oocytes for his group's experiments and others had been paid for their donations (*Science*, 2 December, p. 1402).

Katrina Kelner, *Science* deputy editor for life sciences, says it appeared that the duplicate panels were not part of the original submission but had been sent in response to a request for high-resolution images after the paper had been received. "From the information that we have so far, it seems that it was an honest mistake," she says. "We have no evidence that there was any intent to deceive."

In May 2005, Hwang and his colleagues reported that they had produced 11 new human embryonic stem (ES) cell lines that carried the genetic signature of patients with diabetes, spinal cord injury, or a genetic blood disorder (*Science*, 20 May, p. 1096). The paper not only seemed to validate the group's claim a year earlier that it had created a single cell line from a cloned human embryo, but it also reported a huge increase in efficiency for the technique. In the first paper, researchers said they produced one cell line from 230 tries, but in the second, they claimed they produced a cell line in about one of 15 attempts.

The figure in question is supposed to show patterns of expression for a range of ES cell markers in the 11 cell lines. But it contains four pairs of apparently duplicated images, even though they are labeled as showing different cell lines. Gerald Schatten of the University of Pittsburgh in Pennsylvania, who was the corresponding author on the paper and provided the high-resolution images to *Science*, declined to comment. A university spokesperson said that the university's office of research integrity had begun an investigation. Schatten and his lab members are cooperating, she said, "and are carefully going through the data we have access to to determine how it could have happened." She said Schatten would not comment during the investigation, which might last 6 months.

Rudolf Jaenisch of the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts, says he still has confidence in the reported results. "This is an extremely important study, and I have no reason whatsoever to question any of the published data," he says.

Kelner says the journal will issue a correction once the editors are satisfied they understand what had happened. **–GRETCHEN VOGEL**

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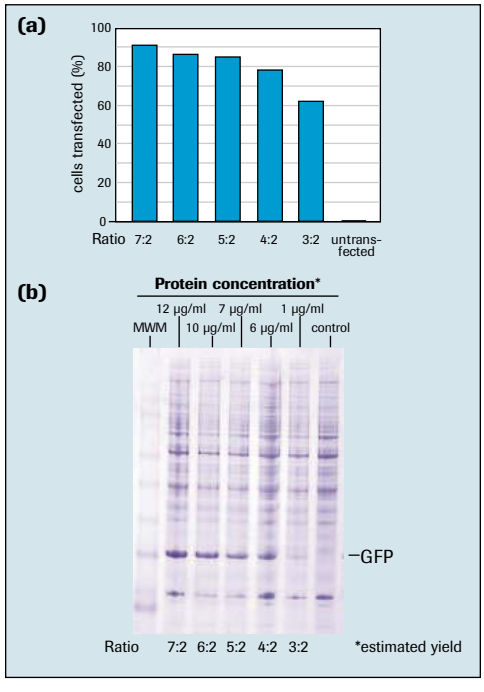

Figure 1: GFP expression in HEK-293 EBNA cells. HEK-293 EBNA suspension-adapted cells were transfected with plasmid DNA for GFP following the recommended protocol, using ratios of 7:2, 6:2, 5:2, 4:2, and 3:2 (µl FuGENE® HD Transfection Reagent:µg plasmid DNA). The percentage of cells transfected (a) was determined 28 hours post transfection and quantity of GFP protein (b) was estimated from the Coomassie Blue-stained gel at 72 hours post transfection.

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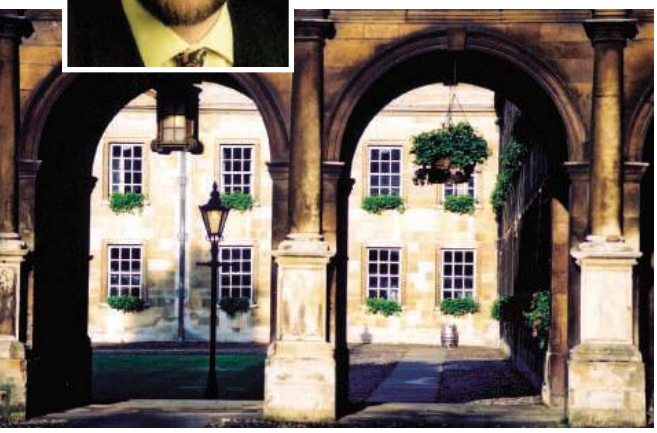
INTELLECTUAL PROPERTY

Cambridge University Reins In Faculty Patents

CAMBRIDGE, U.K.—Computer scientist Ross Anderson would like to be free to patent his own inventions and make private deals, even though he's a university employee. The last thing he wants is "bureaucrats" getting in his way. So far he's been lucky: He works for the University of Cambridge, which has given him and other staff members tremendous leeway—even permitting them 100% ownership of some patents. Very few other universities allow such latitude. But this week, Cambridge is pushing a new policy that would curtail some of that independence and require all inventors on staff to let the university own and more actively manage staff patents.



Hands off. Ross Anderson doesn't want Cambridge University to own his inventions.

Anderson, spokesperson for a group called the Campaign for Cambridge Freedoms (CCF),* sees the new rules as intrusive. He and allies such as molecular biologist Mike Clark, whose income from monoclonal antibody discoveries is a major revenue source for the university, are fighting to retain some of the old ways of doing business. A campus-wide vote this month will determine which side prevails.

The university has been advancing its claims on intellectual property (IP) for several years, prompting fierce debates at every turn. It is setting up a management group called Cambridge Enterprise and wants rules that apply consistently across the board, says university deputy vice chancellor Anthony Minson. So this week, the university sent out ballots to roughly 4000 eligible academic voters to get their approval for its IP rules. Academics will also get to vote on an opposing scheme from CCF that would block some aspects of the university's plans. For example, the dissenters do not want the university to be able to assert ownership of privately sponsored research that is not restricted by the donor. And their plan could prevent the university from intervening in some intramural IP disputes.

A lot of money is at stake, but both sides stress lofty principles. "This is not primarily about money," says Minson, a virologist who helped draw up the university's proposal. "It's about accountability" to taxpayers who help fund the facilities where the research takes place. The goal, he said in an e-mail, is "to achieve fairness by equal treatment of all staff regardless of funding source … and to ensure that the university has the information" it may need to "resolve potential conflicts" among staff and students.

In contrast, Anderson says the battle is really about academic freedom and creativity. Cambridge is "the last university in the U.K. where the academics own [their own patents]," he says. "If the university locks down IP, it will become much more difficult for academics to spin out" ideas into commercial ventures.

Minson disagrees. The university has promised its staff what he believes are "more generous terms than any other university in the U.K." Although the administration intends to claim ownership, it will let independent-minded inventors such as Anderson and Clark do the patenting and negotiate deals themselves if they want to. And he says a sliding-scale formula would return most income to the inventor: 90% below £100,000 a year, dropping to around 30% at £200,000. Because the scheme is flexible, Minson says, "I just don't accept" the argument that a "bureaucracy will sit heavily" on Cambridge's creative spirits.

The referendum is expected to draw about 1500 votes. Anderson says 84 academics have publicly endorsed the CCF amendments, and he believes there are another "several hundred" solid supporters. But university leaders have been selling their plan aggressively within the ranks. The dissenters concede that they're facing an uphill battle.

–ELIOT MARSHALL

* CCF and university statements, respectively: www.freecambridge.org and www.admin.cam.ac.uk/reporter/2004-05/weekly/6001.17.html.

CREDITS: NIGEL LUCKHURST/UNIVERSITY OF CAMBRIDGE; (INSET) R. ANDERSON

ScienceScope

Gifts With Broad Impacts

Not many scientific institutes score $100 million gifts, much less twice. The Broad Institute in Cambridge, Massachusetts, tasked to turn genetic data into medical advances, last week received its second windfall from Eli and Edythe Broad in less than 2 years.

The Broads stipulated with their first grant that the collaboration between the Massachusetts Institute of Technology and Harvard University must spend $10 million a year; the second gift means that the institute will be required to spend $20 million. The institute, which will move into new digs opposite MIT in the spring, has an annual budget of about $100 million, most of which comes from government grants. –ANDREW LAWLER

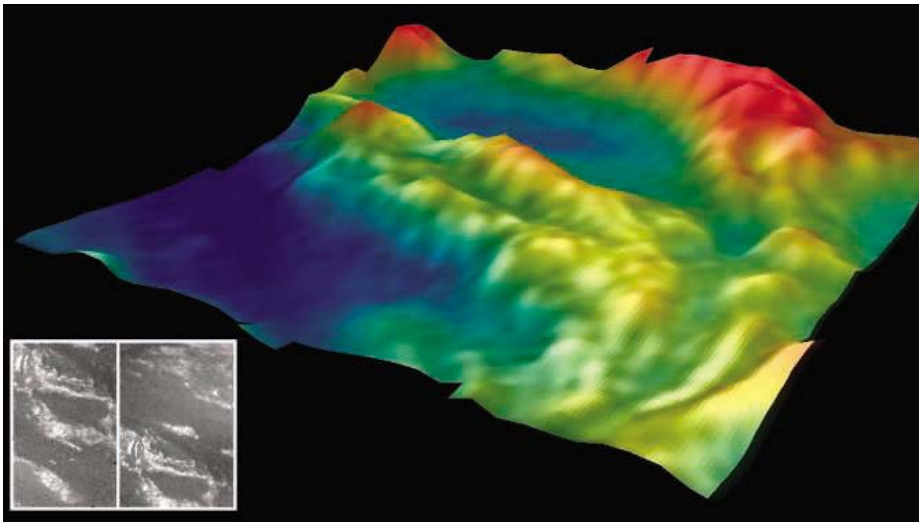
Neuroscientists Without Borders

The Karolinska Institute in Stockholm has been chosen to host a new center to help neuroscientists manage and share their data, organizers announced last week in Paris. Founded by six European countries and the United States, the $1.2-million-per-year International Neuroinformatics Coordinating Facility will foster international collaboration in maintaining databases and analyzing the torrent of data generated by brain scanners and other modern tools. The center will also fund projects to create neuroscience databases and develop computational tools for data analysis and modeling brain function.

–GREG MILLER

Collider Coming Together

Particle physicists settled this week on the basic specs for the International Linear Collider, a multibillion-dollar particle smasher they hope governments in Europe, Asia, and North America will agree to build sometime in the next decade. Researchers in Frascati, Italy, finalized a document that sets general parameters, such as the strength of the particle-accelerating electric fields in the 40-kilometer-long tunnels. Over the next year, physicists will design the many parts of the machine, which would collide electrons and positrons. "Before [this document], it wasn't clear that we were all designing the same thing," says Barry Barish of the California Institute of Technology in Pasadena, who leads the design effort. Researchers will also calculate the cost; previous estimates have run as high as $12 billion. –ADRIAN CHO



Alien world. Peaks and dark plains on the surface of Titan were snapped by Huygens during its descent on 14 January 2005.

SPACE SCIENCE

Europe Trumpets Successes on Mars and Titan

PARIS—Less than a week before it has to persuade European governments to approve its budget for the next several years, the European Space Agency (ESA) has been parading some of its achievements in 2005. These include the first batch of published results from the Huygens probe to Saturn's enigmatic satellite Titan (the most distant landing ever accomplished) and tantalizing glimpses of underground water from the Mars Express mission's ground-penetrating radar—the first subsurface view of another world. "There have been many nail-biting moments, but 2005 has been a great year for European space science," says ESA science director David Southwood.

On 14 January, after hitching a 7-year ride on NASA's Cassini spacecraft bound for Saturn, Huygens descended through Titan's murky atmosphere and landed on an alien but weirdly familiar world in which the rocks are made of water ice and monsoons of liquid methane rain down from the orange sky. Many of Huygens's results have already been released (*Science*, 21 January, p. 330; 28 January, p. 496; 13 May, p. 969; 23 September, p. 1985), but the first comprehensive set of scientific papers, published last week on *Nature*'s Web site, fills in the details. They indicate that Titan—which is larger than the planet Mercury—is a frigid world sculpted by intermittent downpours of methane that carve out valleys and leave tarlike puddles of hydrocarbon goo. Huygens also found evidence for ammonia-spewing cryovolcanoes, detected bolts of lightning, measured wind patterns in the atmosphere, and analyzed the organic-rich airborne dust particles, as well as the reddish surface material.

At a 30 November press conference here, Jonathan Lunine of the University of Arizona's Lunar and Planetary Laboratory in Tucson also presented a detailed comparison of small-scale Huygens descent images and wide-angle Cassini radar maps, obtained during the orbiter's Titan flyby on 28 October. "We've now been able to pinpoint the Huygens landing site to within a few kilometers," he says. It's "kind of surprising," Lunine adds, that the dark, hydrocarbon-rich areas in the Huygens images are also dark in the radar maps, indicating a smooth terrain—very different from the icy cobbles seen by Huygens at its landing site. Unfortunately, Cassini won't have another opportunity to radar-map the landing site until 2008, says Lunine.

In the other ESA success story, another radar instrument, Italy's Mars Advanced Radar for Subsurface and Ionospheric Sounding (MARSIS) on board Mars Express, has provided scientists with a first peek beneath the martian surface (*Science* Express, 30 November 2005, www.sciencemag.org/cgi/content/abstract/1122165). Although Mars Express arrived at the Red Planet 2 years ago, MARSIS was not deployed until last summer because of concerns that unfurling the long radar booms might damage the spacecraft. So far, team member Jeffrey Plaut of NASA's Jet Propulsion Laboratory in Pasadena, California, says he's "absolutely thrilled by its performance." For instance, MARSIS was able to detect radar reflections from the subsurface base of the ice layer close to the planet's north pole, indicating that the deposit is about 1.8 kilometers thick, it contains less than 2% dust, and the underlying crust must be very strong.

Ice-rich material may also fill a 250-kilometer-wide buried crater found in Chryse Planitia at Mars's midnorthern latitudes. "The find of subsurface craters is in itself not surprising," says planetary geologist Michael H. Carr of the U.S. Geological Survey in Menlo Park, California, "but if they are filled with ice, that would be a very interesting discovery, since we don't know where the water went that was present on Mars in its early history." The search for subsurface liquid water may have to wait until next spring, when Mars Express is in a better orbit for detailed radar observations of the planet's low-lying Hellas Basin, where water may be closer to the surface.

France's OMEGA instrument, which maps martian minerals from orbit, has confirmed that the Red Planet must have been wet for extended periods in the distant geologic past. In last week's issue of *Nature*, OMEGA principal investigator Jean-Pierre Bibring of the Institute of Space Astrophysics in Orsay, France, and his colleagues describe how the device found claylike minerals known as phyllosilicates in locations where erosion has exposed very ancient terrain. They date back to an era when liquid water was abundant, some 3.8 billion years ago. "These spots are the most favorable to have hosted the possible emergence of life," says Bibring. "I hope the future European ExoMars astrobiology lander will go there."

Gerhard Neukum of the Free University in Berlin, who heads the camera team of Mars Express, agrees that the planet went dry globally about 3.5 billion years ago. "But locally and regionally, there has been glacial and fluvial activity every few hundred million years or so, maybe until the present time," he says. New images from the High-Resolution Stereo Camera show clear evidence of young glaciers in Deuteronilus Mensae and recent lava flows on the flanks of the Olympus Mons shield volcano. Says Neukum: "Mars is not dead."

Whereas the Huygens mission was over within a few hours of touchdown (its batteries were only designed to last a short time), ESA recently extended the Mars Express mission until November 2007. But according to project scientist Agustín Chicarro of ESA's R&D center in Noordwijk, the Netherlands, the craft's solar-charged batteries will last for at least five more years, and there's enough onboard propellant for another 2 decades. "ESA has never shut down any mission because of money constraints," says Chicarro. "Let's hope they'll continue the tradition."

—GOVERT SCHILLING

Govert Schilling is an astronomy writer in Amersfoort, the Netherlands.

BIOMEDICAL POLICY

U.K. Doubles Stem Cell Funding

Heeding warnings that it risks falling behind, the U.K. government announced on 1 December that it will increase its funding of stem cell research from £50 million to £100 million ($85 million to $170 million) over the next 2 years. But even more is needed if the country is to compete with places such as California, which pledged $3 billion over the next decade, says a new report by the government-appointed U.K. Stem Cell Initiative.

"It's very encouraging," panel chair John Pattison, a former Department of Health director, says about the government's commitment. However, like the panel, which recommends the United Kingdom spend at least £600 million ($1 billion) between 2006 and 2015, he urges the government to do more.

The United Kingdom is already well positioned, the panel notes. It has been home to several important stem cell advances, including the first cloned mammal Dolly the sheep and the world's first stem cell bank. And it has a strict but facilitating regulatory environment. "The U.K. has enthusiastically supported growth of the emerging areas of both embryonic and adult stem cells," says stem cell biologist Roger Pedersen of the University of Cambridge. Both he and the panel emphasize that long-term investment is needed to keep talented researchers from going to the United States, Singapore, or South Korea.

Funding is also needed to reduce the lag between scientific advances and development of medical treatments. Funding agencies give this sort of translational research lower priority, Pattison says. The report recommends that the government establish a public-private partnership to develop stem cell tools for testing the toxicity of drugs. "We have made a good start here in the U.K.," Pattison says, "but additional funding is needed to capitalize on that early investment."

–MICHAEL SCHIRBER

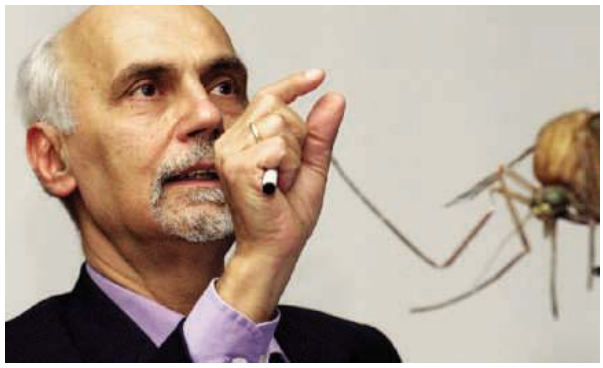
EUROPEAN RESEARCH

ERC Moves Forward Despite Budget Impasse

BERLIN—The long-awaited European Research Council (ERC) now has three veteran science chiefs to guide the agency through its birth.

ERC, designed to fund basic science across Europe, is supposed to award its first grants in 2007. However, high-level disagreements over the E.U. budget have kept scientists guessing about how hard a hit the fledgling body's proposed €1.5 billion yearly budget might have to absorb. Uncertainty notwithstanding, ERC's scientific council last week elected Fotis Kafatos as chair. Kafatos, a molecular entomologist at Imperial College London led the European Molecular Biology Laboratory from 1993 to 2005 and is credited with revitalizing one of Europe's top research institutions. Rounding out the triumvirate are vice-chairs Helga Nowotny, an expert on science and society at the Wissenschaftszentrum in Vienna, and physicist Daniel Esteve of the French Commission for Atomic Energy CEA Saclay.

The three, along with the rest of the science council, are well equipped to fend off political attempts to divert ERC funds to particular fields or countries, says Frank Gannon, president of the European Molecular Biology Organization in Heidelberg. "All signs are that the process is working the way the scientific community wants it to," he says.



This big? Fotis Kafatos, chair of the European Research Council scientific council, hopes political wrangling won't shrink the new agency's budget.

CREDIT: NICOLAS ASFOURI/AFP/GETTY IMAGES

In the meantime, U.K. Prime Minister Tony Blair put forward a budget proposal on 5 December that did nothing to ease researchers' fears. Earlier this year, E.U. officials proposed doubling the overall research budget, to just over €10 billion ($12 billion) per year. But as political disagreements escalated, those proposals took a hit; Blair's compromise would scale back the research budget to closer to €6 billion yearly. Both Kafatos and Nowotny say that to be viable, the ERC will need at least €1 billion per year. European heads of state will meet next week to try again to seal a deal.

–GRETCHEN VOGEL

ScienceScope

Nuclear Pact at Issue

Three Western nuclear powers are hoping that five former Soviet states will listen to their concerns before inking an agreement that would establish a Central Asia Nuclear-Weapon-Free Zone. The problem is language deferring to a 1992 collective security agreement that Russia interprets as allowing for the possible deployment of nuclear weapons in Central Asia during a crisis.

The Central Asia zone would increase nuclear safeguards in Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan and fight trafficking of nuclear materials from Russia. A tentative agreement to create the zone, the world's fifth, was reached in September after 8 years of talks. But in a démarche the next month, the United States, the United Kingdom, and France stated that they "cannot be expected to support the treaty ... if the obligations of existing international treaties take precedence over the obligations of the proposed" nuclear-free pact.

Their concerns have so far blocked final adoption of the treaty. In earlier negotiations, the three powers had an ally in Uzbekistan, which had pushed for a nuclear-free pact to take precedence over the 1992 Tashkent treaty. But a recent downturn in U.S.-Uzbek relations may change Uzbekistan's stance.

–RICHARD STONE

NIH Opens Coordinating Office

The National Institutes of Health (NIH) next month will open a powerful new office meant to coordinate—but not dilute—the agency's sprawling $28 billion research enterprise.

The Office of Portfolio Analysis and Strategic Initiatives (OPASI) is a response to complaints that NIH's 27 institutes and centers have become too unwieldy, as well as a way to plot NIH's future. NIH Director Elias Zerhouni eventually wants to put as much as 5% of each institute's budget into a fund for crosscutting initiatives. But NIH Deputy Director Raynard Kington assured NIH's advisory council last week that the 1.7% share going to the prototype for this effort, the NIH Roadmap, in 2008 won't grow unless NIH receives budget increases that at least match rising costs. Funds will be disbursed by institutions, not OPASI, reassuring biomedical research advocates. "There's a lot of support" for the office's analytical role as well, says David Moore of the Association of American Medical Colleges.

–JOCELYN KAISER

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NIH TRAINING GRANTS

Universities May Have to Pay More In Support of Graduate Training

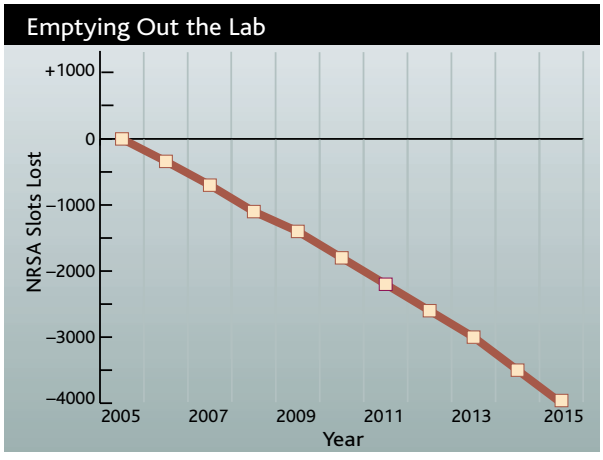
National Institutes of Health (NIH) officials regularly say that training the next generation of biomedical scientists is a high priority for the $28 billion agency. But last week at a town hall–style meeting in Bethesda, Maryland, they conveyed a different message to universities: Pony up more of your own resources to shoulder the costs of training, or face a decline in the number of graduate students and postdocs that NIH supports.

The meeting explored a fiscal crunch facing the Ruth Kirschstein National Research Service Award (NRSA) program, which supports more than 17,000 Ph.D. students and postdocs, primarily through institutional training grants. NIH currently provides the major share of trainees' tuition, paying the first $3000 plus 60% of the remainder, and covers a share of each trainee's health insurance. But faced with steadily rising tuition and health care costs, along with a flat budget, NIH says it must transfer more of the burden to universities or reduce the number of NRSA trainees. If the program's funding doesn't grow, the current formula would result in a loss of "4000 slots by 2015," says NIH deputy director Norka Ruiz Bravo (see graphic).

To ease the problem, the agency is considering three options. The first would retain the existing formula but cap the reimbursable amount at $16,000 to $18,000, roughly the current average subsidy. The second option would provide a fixed allowance—again capped at $16,000 to $18,000. The last would continue the current policy, staying on budget by squeezing both the number of institutional grants and the number of trainees per grant.

Some call for NIH to shift funds into NRSA from other areas. The choices on the table reflect the lack of "an appropriate distribution and management of training and educational funds" within the NIH budget, believes Glen Gaulton of the University of Pennsylvania School of Medicine in Philadelphia. "All three are lousy options," says Robert Simoni, head of biological sciences at Stanford University in California, who nevertheless supports the status quo.

NIH officials defend flat-lining their investment in training. "Prudent policy requires an appropriate balance between training budgets and the funds available for research support," says Ruiz Bravo. But she acknowledges that "an annual loss in training positions would threaten the stability of ongoing programs and impede consideration of training programs in new and emerging scientific fields."



Fewer trainees. NIH projects a loss of 4000 NRSA awards over 10 years if spending remains level.

The proposed ceiling on tuition would force universities to shift funds "away from investment in new investigators and research equipment," complains Linda Dykstra of the University of North Carolina, Chapel Hill. Speaking on behalf of the Association of American Universities, whose 62 members are a mix of public and private institutions, Dykstra favored retaining the current formula and reducing the number of trainees. Most participants from public universities, however, came out in support of a cap, a change that presumably would affect them less than the most-expensive private schools. Based on those who spoke, the audience on the NIH campus appeared evenly divided among the three options.

NIH expects to make a decision on NRSA's future by spring. —YUDHIJIT BHATTACHARJEE

NIH CAREER AWARDS

Young Scientists Get a Helping Hand

Getting that first faculty job represents the end of one arduous journey for a biomedical scientist—and, given the difficulties and cost of establishing a new lab, the start of another. Last week, the National Institutes of Health (NIH) rolled out three initiatives intended to smooth that transition to becoming an independent researcher.

One of them, expected to be finalized by spring, is a 5-year award for postdocs that will provide initial salary support and then convert to a full-fledged research grant once the scientist gains a faculty position. The other two are already being tested: an independent investigator grant program that does not require applicants to submit preliminary data and a process to speed up the resubmission of R01 grant applications by new investigators who fail on their first attempt. NIH officials hope that the three initiatives will help young scientists get their labs up and running more quickly—a goal agency Director Elias Zerhouni calls his "number one priority."

At $250,000 a year, the new transition awards will be more than three times larger than a typical career development award, and they come with an equal amount of institutional overhead compared to the 8% indirect cost rate allowed by the career awards. The goal is to give universities an added incentive to recruit young investigators and provide newly hired faculty members with some breathing room before applying for their first major grant, says Story Landis, director of the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland.

"If you came with this kind of dowry," Landis says, "deans, even in troubled times, should be willing to take a chance [on you]." Biologist Thomas Cech, president of the Howard Hughes Medical Institute in Chevy Chase, Maryland, and chair of a recent National Research Council (NRC) report on fostering independence among young biomedical researchers, calls the award "a wonderful move forward." Landis won't say how many awards NIH plans to give, although Cech says it should be at least 100.

The NRC report inspired another of the initiatives: a new grant competition at the National Institute of Environmental Health Sciences (NIEHS) for investigators lacking enough preliminary data for a full-fledged NIH proposal. NIEHS plans to give out six such grants next year, and other institutes may join in.

A third effort, by the Center for Scientific Review, the NIH unit that evaluates grant applications, aims to speed up the turnaround time for new investigators so they can resubmit a revised application by the next triyearly deadline. Beginning in February, 40 study sections will meet earlier than usual to review submissions from first-time applicants and provide written evaluations within a week. Applicants will also receive 20 extra days to file a resubmission. —YUDHIJIT BHATTTACHARJEE

SOURCE: NIH

A year after the Indian Ocean tsunami, nations along the coast have created the framework for a regionwide warning system

Girding for the Next Killer Wave

BANGKOK—At 10:42 p.m. on Sunday, 24 July, a strong undersea earthquake rattled the Nicobar Islands, 660 kilometers west of Thailand. Minutes after the 7.3-magnitude quake struck, Thailand's National Disaster Warning Center (NDWC) swung into action. Director Plodprasop Suraswadi appeared on national television to issue the country's first-ever tsunami watch: If the quake generated a tsunami, he warned, the wave would hit the resort island of Phuket at 12:12 a.m.

The advisory, broadcast on all Thai channels, was not an evacuation order. But with memories of the devastating 26 December 2004 Indian Ocean tsunami still fresh, hundreds of people on Phuket and along the Andaman Sea coast of the Malay Peninsula grabbed what they could and fled to higher ground. A crucial piece of data came in just before midnight: Off the Similan Islands, 50 kilometers from the Andaman coast, a tide gauge measuring sea level had barely bobbed. There would be no tsunami. Suraswadi took to the airwaves to sound the all clear.

If the NDWC had been operational last year, thousands of lives might have been spared. The Indian Ocean tsunami killed 5396 people in Thailand; another 2951 people are still listed as missing. Warnings could have saved countless lives elsewhere. Some 230,000 people died in a dozen nations, including 168,000 in Indonesia's Aceh province at the tip of the island of Sumatra.

The lesson in ill-preparedness has sparked a mad dash to create a tsunami warning system for the Indian Ocean. As the first anniversary of the disaster approaches, an alarm network is beginning to emerge—a loose web of deep ocean sensors, tide gauges, and seismic stations operated by individual countries, along with mechanisms for sharing data and disseminating public warnings. Last month, for example, Indonesia, the country deemed most vulnerable to the next big Indian Ocean tsunami, deployed two sea-floor pressure sensors and associated buoys, the vanguard of a 10-sensor network. "We want to show the world that we are ready," says Jan Sopaheluwakan, deputy chair of earth sciences at the Indonesian Institute of Sciences in Jakarta.

By establishing warning centers, Thailand and other countries have begun to fill a lethal void. They will issue tsunami advisories more often, and in most instances the resulting wave will be puny or nonexistent—ratcheting up anxiety and prompting people to flee the seaside needlessly. "People are going to have to be understanding about this," says NDWC's Cherdsak Virapat, director of Thailand's International Ocean Institute in Bangkok.

Big heave. The 26 December 2004 quake exposed coral off Simeulue Island in Aceh province. Dudi Prayudi of the Indonesian Institute of Sciences and Aron Meltzner of Caltech measure the uplift at 1.2 meters.

CREDITS (TOP TO BOTTOM): PAULA BRONSTEIN/GETTY IMAGES; KERRY SIEH/TECTONICS OBSERVATORY, CALIFORNIA INSTITUTE OF TECHNOLOGY

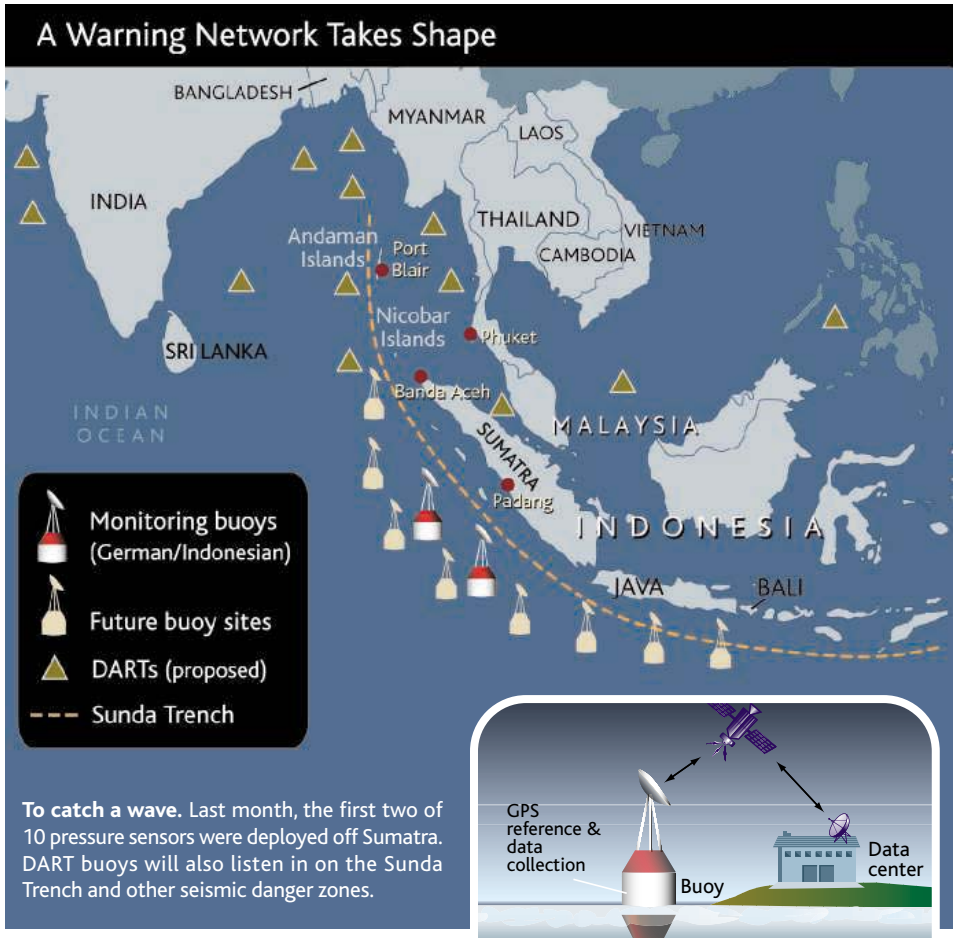
Asleep at the wheel

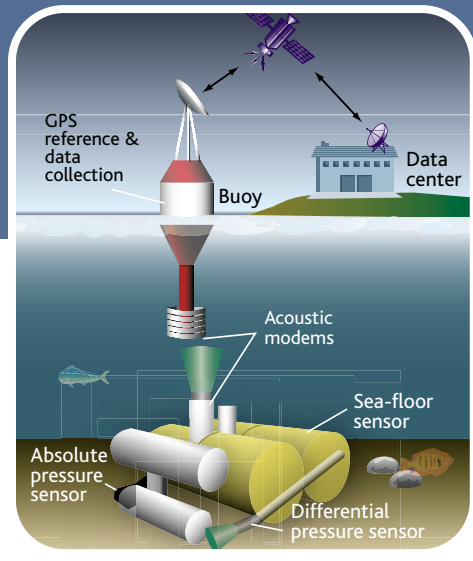
The Indian Ocean tsunami last December caught governments woefully off-guard. The trigger was a monster earthquake at a magnitude of 9.3, centered west of Aceh, on the northwestern tip of Sumatra. The quake struck at 7:59 a.m. Indonesia time, and within 40 minutes a wave, the first of three destructive moving mounds of seawater, had inundated the city of Banda Aceh. Nearly 2 hours after the earthquake, the first wave barreled into Phuket and neighboring seaside provinces of Thailand. It was a Sunday morning; most government offices were closed. Staff in a meteorological office in northern Thailand saw the seismic report but had no idea that a tsunami might be imminent, says Virapat. "Every year, someone would ask, 'What should we do if there is a tsunami?' " The possibility seemed remote, he says.

Minutes later, the Nicobar Islands, including an Indian Air Force base at Car Nicobar, were pummeled. It took another 90 minutes for the tsunami to travel across the Bay of Bengal. But no one sounded the alarm, and the waves claimed 15,000 in India and 31,000 in Sri Lanka.

Stunned by the realization that the human toll need not have been so high, representatives of Indian Ocean nations met in Bangkok last January to begin planning for a tsunami alert system. Discussions bogged down over who would host a regional warning center. By spring it was clear that each country would establish its own center, although the Intergovernmental Oceanographic Commission of UNESCO was invited to coordinate an Indian Ocean Tsunami Warning and Mitigation System, the subject of an IOC meeting next week in Hyderabad, India. It is expected to cost $200 million to bring the system online over the next few years.

IOC is counting on five nations—Australia, India, Indonesia, Malaysia, and Thailand—to cover the entire Indian Ocean, with other nations enhancing the coverage. "No single nation can protect itself or provide protection to others alone," says IOC executive secretary Patricio Bernal. Real-time data will stream into one or more "subregional centers," he says, where it will be rapidly processed and fed back to national warning centers, which would decide on their own whether to issue tsunami advisories to their citizens. India continues to resist sharing real-time seismic and tidal data, out of concern that certain information could compromise its nuclear weapons program (see sidebar, p. 1604). Nevertheless, a basic Indian Ocean–wide system is expected to be in place by July 2006, says physical oceanographer William Erb, head of IOC's office in West Perth, Australia. More advanced assets, such as the deep-ocean tsunameters, will come later.





To catch a wave. Last month, the first two of 10 pressure sensors were deployed off Sumatra. DART buoys will also listen in on the Sunda Trench and other seismic danger zones.

ILLUSTRATIONS: L. CREVELING/*SCIENCE*; (INSET) ADAPTED FROM *DEUTSCHE WELLE*

A hazardous way ahead

As governments gear up to cope with the next tsunami, scientists have pieced together a vivid picture of the shattered Sunda fault off the island of Sumatra—and an idea of what could be in store for the region.

The December quake's 1300-kilometer-long offshore rupture shunted stress southward beneath the sea floor, prompting seismologists to warn that the section of fault adjacent to Sumatra could be the next to fail. No one knew how close to failure that segment was, but geophysicists John McCloskey, Suleyman Nalbant, and Sandy Steacy of the University of Ulster in Coleraine, Northern Ireland, warned in the 17 March issue of *Nature* that the fault had not broken since 1861. That was enough time to build up energy for a sizable earthquake. On 28 March, it struck at a hefty magnitude 8.7.

As in December, the region was unprepared. The U.S. National Oceanic and Atmospheric Administration's (NOAA's) Pacific Tsunami Warning Center (PTWC) in Ewa Beach, Hawaii, registered the earthquake 8 minutes after it occurred and issued a tsunami bulletin 11 minutes later. Without any deep ocean sensors or tide gauges off Indonesia, "it took hours to determine if, in fact, [the earthquake had] created a tsunami," notes David Johnson, director of NOAA's National Weather Service. The bang ended with a whimper: The wave recorded at Cocos Island was just 23 centimeters. The tsunami was trivial in large part because the quake had heaved the sea floor upward beneath islands and surrounding shallow waters, not in deep waters where motions can spawn massive waves (*Science*, 15 April, p. 341).

Now the Ulster group, joined by paleoseismologist Kerry Sieh of the California Institute of Technology in Pasadena, is warning that the risk is moving southward. The next section of fault down the line—from 1°S to 5°S, offshore of the Sumatran city of Padang—could well be poised for disaster. This segment last failed in 1833; the accumulated stress could drive a quake larger than magnitude 8.5. A subsequent tsunami would threaten a million people along 500 kilometers of low-lying Indonesian coast.

New findings underscore the risk. Earlier this week, at the fall meeting of the American Geophysical Union (AGU) in San Francisco, California, the Ulster group, with colleagues at the National Institute of Geophysics and Volcanology in Rome, reported preliminary computer simulations of possible south Sumatra tsunamis. They first modeled a range of possible earthquakes of magnitude 8.0 to 9.0 and then used the resulting sea-floor movement to drive a model of tsunami wave generation. Initial results show that the coast from Padang south could be devastated.

Elsewhere around the Indian Ocean, the tsunami risk from a massive quake off Padang is relatively low. The new simulations suggest that farther from Sumatra, most wave energy would be dissipated in the vast emptiness of the ocean. Here, the fault bends along the southward-facing Indonesian archipelago in a way that a far-traveling tsunami would be directed away from December's hard-hit targets: Thailand, India, and Sri Lanka.

Other stretches of the deep-sea Sunda fault are less worrisome. At the AGU meeting, seismologists Emile Okal and Seth Stein

of Northwestern University in Evanston, Illinois, reported that, based on the behavior of similar faults around the Pacific, the continuation of the fault to the south off the Indonesian island of Java is not likely to generate a devastating magnitude-9 quake. And to the north of last December's break, the fault hasn't even produced magnitude 7s. "Our guess would be you're not going to have big, thrusting earthquakes there" of the sort that generate a tsunami, says Stein. Instead of the tectonic plate thrusting down into the mantle and shoving up the sea floor to generate a tsunami, he says, to the north the plates probably slide by each other San Andreas–style, without triggering tsunamis.

Round-the-clock surveillance

With south Sumatra identified as the area of high tsunami risk, experts are hoping to get a better fix on how far inland tsunamis of various sizes would run, while devising evacuation plans and reinforcing infrastructure. The models have "spurred us to get to work," says Jose Borrero of the Tsunami Research Center at the University of Southern California (USC) in Los Angeles, who charted the ebb and flow of last December's tsunami based on his field surveys and satellite imagery (*Science*, 10 June, p. 1596). His team is now modeling inundation scenarios in the Padang region.

Indonesia is taking the threat seriously. Padang's vulnerability is "bitter news" for the local population, says Sopaheluwakan. "To prevent Padang from becoming the next disaster," he says, the government is working with local authorities to develop a comprehensive evacuation plan. If an earthquake of magnitude 6 or larger occurs in the Sunda Trench, an immediate evacuation order will be broadcast for any coastal area that a wave would strike within 30 minutes of the quake, Sopaheluwakan says.

Indonesia won't rely solely on seismic signals in making a call on a tsunami. Last month, scientists deployed the first two seafloor sensors of the German Indonesian Tsunami Early Warning System. The devices, whose development was spearheaded by the National Research Centre for Geosciences in Potsdam and the Leibniz Institute of Marine Sciences in Kiel, measure sea-floor vibrations and pressure changes in the water column. Data are transmitted by acoustic modem to a buoy linked by satellite to Jakarta. The system is designed to alert Jakarta within tens of seconds of an oncoming tsunami.

After the crew on the *Sonne*, a German research ship, positioned the first sensor and buoy on the Sunda Trench southwest of Padang on 20 November, they made a port call in Padang. If a tsunami were heading there, the area would be tough to evacuate. "Only three streets lead out of the city to higher ground. On a normal day, those three streets are usually full to overflowing with traffic," expedition scientist Ernst Flüh, a geophysicist at the Leibniz institute, noted in a Web log on the *Deutsche Welle* Web site. Locals he met were placing high hopes in the German sensors. "Over and over again we had to explain that one or two buoys do not make an early warning system," he wrote.

The second buoy and sensor set was deployed northwest of Padang on 24 November. The system won't be operational until another eight are installed over the next 2 years. They will run in a line off the coast from Banda Aceh to Bali, each separated by at most 200 kilometers. The German government is footing the system's € 45 million bill.

A network of deep ocean tsunami buoys operated by other countries will monitor the rest of the Indian Ocean. The U.S.-made Deep-Ocean Assessment and Reporting of

A Dead Spot for the Tsunami Network?

NEW DELHI—The budding regional tsunami warning system in the Indian Ocean may get little useful information from one key partner: India. The Indian government insists it will not release seismic recordings in real time, because if it were to resume nuclear testing, the detailed seismic signatures would immediately be broadcast to the world. Officials have also told *Science* they will not share online tide-gauge data, out of concern that such information could aid an aggressor attempting an invasion by sea. Delays in pinpointing an earthquake's location or confirming wave propagation could delay a tsunami warning.

India's status as data holdout contrasts with its commitment to creating the region's most ambitious warning center for tsunamis and cyclone-generated storm surges. Under a $30 million plan, India will increase the number of its tide gauges fivefold and more than triple its seismic stations from 51 to 170. The first of 17 new broadband seismic stations came online at Port Blair, capital of the Andaman and Nicobar Islands, last May. And India plans to deploy up to 12 tsunameters—Deep-Ocean Assessment and Reporting of Tsunamis (DART) buoys and sea-floor sensors that detect pressure changes in the water column—although it is not expected to share these readings in real time either. Data will feed into a nerve center in Hyderabad, planned to be operating by September 2007.

Indian scientists predict that the new tools, coupled with inundation models under development at the National Institute of Oceanography in Goa, should reduce the time required to assess tsunami risk after an earthquake from 40 minutes to 10. To minimize false alarms, Indian officials say that a tsunami warning will be issued after a major quake only if a significant pressure increase is registered by a DART, once these are in place in the Bay of Bengal, the Arabian Sea, and the southern Indian Ocean.

Sharper hearing. India has fired up its first new broadband seismometer, in Port Blair.

India's reluctance to share data could come back to haunt it. India has refused to hook up its vaunted array of seismometers to the Global Seismographic Network, 128 stations that record temblors and listen for signatures of nuclear detonations to help verify compliance with the Comprehensive Test Ban Treaty, which India has not joined. The seismic network is crucial to quickly pinpointing a quake's magnitude and location—and for analyzing tsunami threats.

Some Indian officials acknowledge a risk. "Our existing policy of not sharing online seismic data has to change," says Valangiman Subramanian Ramamurthy, a nuclear scientist and secretary of the Department of Science and Technology. He says India is reassessing its relationship with international networks, and India may agree to divulge data on earthquakes greater than 5 on the Richter scale in "near–real time." That would help, but near–real time equates to a roughly 40-minute lag as Indian experts process data before releasing it.

Earlier this year, some tsunami experts were highly critical of India's policy (*Science*, 28 January, p. 503). But concerns have been eased by ongoing efforts to bolster seismic stations elsewhere in the region and by the prospect of DARTs managed by other countries. "I am less pessimistic now," says Costas Synolakis of the University of Southern California in Los Angeles. "India's [seismic] recordings are not as essential for early warning, particularly for sources 'far' from India," he says. Maybe not—if a killer wave doesn't come before the rest of the Indian Ocean states bring their new instrumentation on line.

—PALLAVA BAGLA

CREDIT: P. BAGLA

Compounding the tragedy. Anguish over loved ones lost in the December tsunami was one trigger for PTSD.

In the Wake: Looking for Keys to Posttraumatic Stress

BANGKOK—Last December's tsunami left a trail of shattered families and anguished survivors. Thousands of victims in the region are thought to suffer from posttraumatic stress disorder (PTSD), whose symptoms include flashbacks, panic attacks, amnesia, and out-of-body sensations. Now, in what's billed as the largest study of its kind, Thai researchers have embarked on a hunt for genes that may leave people vulnerable to PTSD.

Most previous PTSD studies involved victims who had endured traumas of varying duration and intensity: witnessing torture, for example, or experiencing a bomb blast. This work has not nailed vulnerability genes as yet, although it has found candidates. An advantage of the Thai government–funded study, organized by the Thailand Center of Excellence for Life Sciences (TCELS), is that most victims share a common genetic heritage and were exposed at the same time to the same stimulus, namely the tsunami wave. A pharmacogenetic component of the study aims to assess whether an individual's response to drug therapy depends on his or her genetic makeup. It's "a highly novel and potentially unprecedented approach," says Robert Malison, a psychiatric researcher at Yale University.

Beginning in February, psychiatric epidemiologist Nantika Thavichachart of Chulalongkorn University and colleagues interviewed more than 3000 adults on the coast. "Victims were committing suicide more than 3 months after the tsunami," says TCELS president Thongchai Thavichachart. About 600 were diagnosed with chronic PTSD. Researchers drew blood from victims, healthy siblings, and unrelated individuals.

In the $3 million study's next phase, to begin in early 2006, researchers will create "immortalized" cell lines from each blood sample and then fish for gene variations, or alleles, that may underlie susceptibility to PTSD. A team led by geneticist Verayuth Praphanphoj of Thailand's Department of Mental Health will target about 20 genes by zeroing in on DNA markers called single-nucleotide polymorphisms. His group will also take a second tack, trawling for genetic signals in a whole-genome association study of a few hundred individuals.

Experts suspect that several genes are involved in susceptibility to PTSD, considering the constellation and variability of symptoms, some of which overlap with those of anxiety disorder and depression. Preliminary results are due in late 2006. Yale's Joel Gelernter, for one, has high expectations. "There's a very good chance" that the study will pinpoint more candidate PTSD genes, he says. **–R.S.**

Tsunamis tsunameters—each a buoy and an associated bottom pressure sensor—already serve as sentinels for the PTWC in Hawaii. It's the only such device that's been "tried and tested," notes IOC's Erb. At a price tag of $250,000 per buoy and a design life of 1 year, the network won't come cheap, nor will it come quickly: The U.S. factory that produces the buoys was inundated by Hurricane Katrina, so production is lagging, sources say. Thailand plans to buy two and have them in place in the Andaman Sea by early 2007. India expects to deploy up to a dozen, and Malaysia will place three more in the Straits of Malacca, the South China Sea, and the Sulu Sea.

Some experts contend that investing heavily in high-tech tsunameters such as these, the sexiest and costliest components of the warning systems, is overkill. They say seismographs and tide gauges, coupled with heightened vigilance, are sufficient for most countries. But everyone wants new technology.

Indian Ocean nations meanwhile are upgrading or adding seismic stations and sharpening their ability to map earthquake hazards and analyze data. Thailand, for example, plans to triple the number of its digital stations to 45 by the end of 2008. Countries are also installing digital tide gauges. Before the tsunami, Malaysia's shore-hugging gauges could not transmit data in real time. It is now installing six gauges on far-flung islands that will transmit data to Kuala Lumpur by satellite and increase warning times by minutes. Through IOC, the United States is kicking in $16.6 million over 2 years for these efforts, primarily in India, Indonesia, the Maldives, Sri Lanka, and Thailand.

The most valuable legacy of the 26 December 2004 tsunami may be the national disaster centers that countries are setting up to monitor and act on the data that will be pouring in. India plans to have its tsunami early warning center in Hyderabad up and running by fall 2007. Thailand's NDWC, opened on 30 May, features a 24-hour operations room with live feeds of seismic, tide gauge, and other data from around the Indian Ocean and from Japan and the United States, banks of televisions tuned to news stations, and clusters of desks where analysts are primed to sound the alarm. "Now we have all the information we need to forecast tsunamis," says NDWC geologist Passkorn Kunthasap.

With input from PTWC experts, NDWC scientists have designed a simple schematic for making snap decisions. For offshore earthquakes registering 7.0 to 7.7 on the Richter scale, the center will issue a tsunami watch. A stronger earthquake will trigger a warning and immediate evacuation order. Thailand has recently erected three warning siren towers on Phuket and the peninsula, with plans for 62 more next year.

An open question is whether the national centers "will have the resources and stamina to stay active and alert for what amounts to from now to eternity," says Costas Synolakis, director of USC's Tsunami Research Center. If the centers are devoted solely to their raison d'être—watching for a tsunami that may not come for generations—political and financial support could melt away. "In several years, people would forget and get lax," says Erb. IOC has been urging nations to broaden their mission to a number of natural hazards.

Thai officials have taken that to heart. They hope NDWC will stimulate a more rapid response to flooding, which each year claims dozens of lives and inflicts about $750 million in economic losses, roughly equal to the damage to infrastructure and lost tourism revenue from last December's tsunami. But as the first anniversary of the deadly wave approaches, NDWC and its sister centers will at least have a palliative effect. "We're on watch 24 hours," says Admiral Thaweesak Daengchai, NDWC's executive manager. "And we're not afraid anymore."

–RICHARD STONE AND RICHARD A. KERR

With reporting by Pallava Bagla in New Delhi.

CREDIT: PAULA BRONSTEIN/GETTY IMAGES

Piggyback. If the IPT strategy works, antimalaria drugs could be delivered to infants at the same time they receive vaccinations for childhood diseases.

Will a Preemptive Strike Against Malaria Pay Off?

Researchers are trying to determine whether routinely treating children for malaria before they contract it will save lives without promoting drug resistance

The fight against malaria is famously frustrating. A vaccine is still years away, drug resistance is on the rise, and mosquito-thwarting bed nets, although effective, have proved difficult to get to the people who need them. Now researchers are testing a bold new strategy aimed directly at protecting malaria's most likely victims: infants and young children. Akin to a preemptive strike, the strategy involves giving antimalaria drugs routinely to infants regardless of whether they are infected with malaria parasites.

Treating hundreds of millions of children for a disease they might not have flies in the face of standard public health practice. But evidence so far suggests that this simple and inexpensive treatment, called IPT for intermittent preventative treatment, may significantly slash the disease burden in young children. Nearly 1 million children die each year of the disease.

There is some precedent for the strategy. The World Health Organization (WHO) already recommends that all pregnant women in malaria-affected regions receive IPT. The agency says that whether an expectant mother is infected or not, she should receive one dose of malaria medicine in the second trimester and another in the third. But some malaria experts question whether the costs and benefits were weighed carefully enough before the practice became official policy. In particular, some worry that such large-scale interventions could backfire by promoting drug resistance. "We can do better" to ensure that an investment in IPT in infants will pay off in terms of lives saved, and that it will also avoid causing harm, says David Schellenberg of the Ifakara Health Research and Development Centre in Kilombero, Tanzania.

In an effort to weigh the costs and benefits as quickly as possible, researchers in 2003 formed the IPTi consortium. (The 'i' is for infants.) The group, which includes WHO, UNICEF, and scientists from 14 institutions in 11 countries, received $28 million in funding from the Bill and Melinda Gates Foundation. By coordinating trials and sharing data, the consortium hopes to have enough hard evidence to be able to recommend a policy for whether and how to implement IPTi by the end of 2006. At a meeting* of malaria researchers last month in Yaounde, Cameroon, IPTi was high on the agenda, as consortium members presented new results from one of the half-dozen trials under way across Africa.

* Fourth Multilateral Initiative on Malaria Pan-African Malaria Conference, Yaounde, Cameroon, 13–18 November.

Prevention on the cheap?

One of the key advantages of IPT for expectant mothers is that it can piggyback on existing public health programs by treating women when they visit health clinics for routine antenatal checkups. Several studies have shown that just two treatments with a standard malaria drug pair called sulfadoxine-pyrimethamine (SP) is as effective at preventing malaria complications such as maternal anemia and low birth weight as is more frequent prophylaxis, though much cheaper and easier to administer. The hope is that infants, who would receive antimalaria drugs at the same time they receive vaccinations against polio, diphtheria, and measles, would also benefit from routine intermittent treatment.

The first data on IPT in infants—which helped inspire the formation of the consortium—were remarkable. In 2001, Schellenberg and his colleagues reported that in a study of 700 babies in Tanzania, IPTi cut rates of clinical malaria by almost 60% compared with rates in infants who received a placebo. Another Tanzanian study in 2003 showed that IPTi reduced malarial fevers by 65% in the first year of life.

But more recent studies suggest that such dramatic results can't be expected everywhere. In a trial of nearly 1500 infants in Ghana, described in October in the *British Medical Journal*, treatment cut malaria episodes by just 25% compared to a placebo. Hospital admissions for anemia, one of the most dangerous malaria complications, were 35% lower in the treatment group.

One explanation for the different findings may be the patterns of disease transmission in the two study areas, says Brian Greenwood of the London School of Hygiene and Tropical Medicine, who helped lead the Ghana trial. At the Tanzanian study site, malaria spreads at a relatively low rate year-round. At the site in Ghana, the disease is transmitted during the 6-month rainy season, when residents face about 10 times the rate of infective mosquito bites as faced by those in the Tanzanian study. Greenwood notes that for a subset of Ghanan babies who received their first two doses during the rainy season, results were nearly as good as those in Tanzania; it reduced clinical cases of malaria by 52% and anemia by 72%.

But mosquito bite rates and differing seasons of infection can't explain all the differences seen in IPTi trials. Results from a trial in Mozambique, first reported last

CREDIT: HOSPITAL CLINIC BARCELONA

month in Yaounde, "are not as exciting as we'd hoped for," admits Andrea Egan of the University of Barcelona in Spain, who coordinates the IPTi consortium. A study of 1500 infants, also living in an area of moderate year-round transmission, showed a 22% reduction in clinical malaria rates compared to rates in babies who received a placebo but no difference in anemia rates.

Egan suspects differences in both bed net use and nutrition contributed to the smaller effect. More than half the population in the Tanzanian trial slept under bed nets, she says, whereas in Mozambique, bed net use was almost nil. In addition, in both Ghana and Tanzania, the treatment and control groups received a routine iron supplement, whereas babies in Mozambique did not. Egan speculates that babies in Mozambique might have had such high baseline rates of anemia that protecting them from malaria didn't make a noticeable dent. Consortium members expect to know more soon. Three studies nearing completion, one in Gabon and two in Ghana, are in part designed to elucidate how environment and epidemiology affect IPTi, says Peter Kremsner of the University of Tübingen in Germany, who is helping direct the trial in Lambaréné, Gabon.

First, do no harm

Perhaps the biggest concern about IPTi, however, is whether it could backfire by increasing the malaria parasite's resistance to medications. Drug resistance is one of the most serious problems in the fight against malaria, rendering many of the cheapest and safest drugs ineffective in curing the disease. Indeed, this week researchers reported in *The Lancet* the first evidence for resistance to artemisinin-based drugs, the newest therapy against parasites that can evade other drugs (see sidebar).

In many areas, resistance to the drug combination SP is already well established. Cheap and safe, SP remains a first-line defense against the disease. It is also the first choice for IPTi. Giving the drug to otherwise healthy children might not necessarily increase SP resistance, notes Egan. If the approach succeeds in reducing clinical malaria rates, she says, overall use of the drug might also decline, and resistance rates could even fall. Answers should come from a consortium-sponsored trial involving 12,000 infants in Tanzania that is monitoring rates of resistance as IPTi is introduced.

Some researchers are also worried that IPTi might leave infants more vulnerable to malaria later in their lives. For children living in malaria-endemic areas, early infections are something of a mixed blessing. Although they can be deadly, infections seem to confer some immunity, protecting the babies who survive from becoming seriously ill when infected later. If that process is interrupted, the disease might be delayed but not prevented.

Researchers watching for the so-called rebound effect have reported mixed results. Schellenberg and his colleagues reported in April in *The Lancet* that children in Tanzania who had received IPT as infants still had significantly lower rates of malaria through age 2. The researchers suggest that IPT might actually be helping boost the body's natural defenses against the disease by giving children a head start in fighting off mild infections. But in Ghana, again, the results are less encouraging. Overall rates of malaria went up slightly among IPT-treated children between ages 16 and 24 months, although episodes of cerebral malaria, the most serious form of the disease, decreased.

Nevertheless, consortium members are largely optimistic that studies will support expanding IPT to infants. Reported side effects have been minimal, and even the 22% reduction in malaria among infants in Mozambique is "still very positive," Egan says. Says Kremsner, "If there are soon six and seven studies showing protection, that counts. If that goes along with considerable safety and good tolerability, the policy decision becomes fairly straightforward."

–GRETCHEN VOGEL

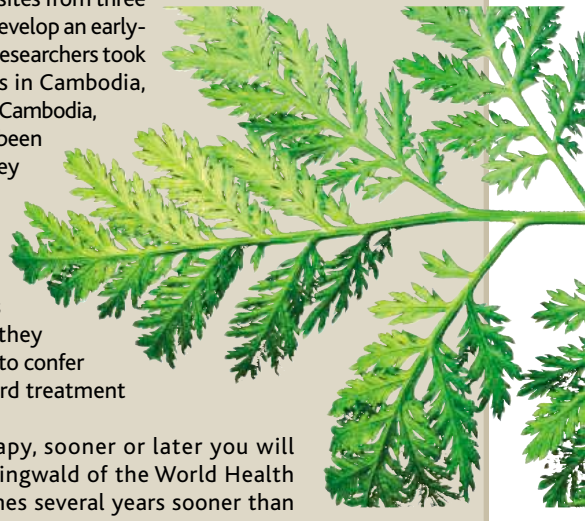
Cracks in the First Line of Defense

The wonder drugs have a weak spot. This week, scientists report the first evidence that the malaria parasite has developed resistance to artemisinin-based drugs, which had been hailed as the last best hope against parasites that can already elude other treatments. So far, the evidence comes just from lab tests of parasites isolated from infected people; no patient has died of artemisinin-resistant malaria. But researchers say the observation is an urgent reminder that the compound and its relatives, just beginning to be employed widely around the world, could fail if not used carefully.

Based on extracts from the sweet wormwood plant *Artemisia annua*, used for centuries in Chinese traditional medicine, artemisinin and its derivatives such as artesunate and artemether had seemed almost invincible. Even in areas where multidrug-resistant parasites render most other malaria medications useless, treatments containing artemisinins routinely cure 90% of patients within days.

Because the compounds are powerful and fast-acting, scientists had hoped that they might pack such a wallop that resistant strains would be slow to appear. To be doubly safe, officials have stressed the importance of using the compounds only in tandem with other drugs, an approach called artemisinin combination therapy (ACT).

The importance of that ACT strategy is highlighted in the 3 December issue of *The Lancet*, in which Ronan Jambou and his colleagues at the Institut Pasteur in Dakar, Senegal, compared the effects of various drugs on malaria parasites from three different parts of the world. In an effort to develop an early-warning system for signs of resistance, the researchers took blood samples from 530 malaria patients in Cambodia, French Guiana, and Senegal. In samples from Cambodia, where use of artemisinin-based drugs has been tightly regulated as part of ACT therapy, they found no evidence of resistance. But in samples from Senegal and French Guiana, where artemisinins are either unregulated or approved for use without other drugs, lab tests revealed the presence of parasites that could survive the drug. In addition, they identified several mutations that are likely to confer the resistance. "This is the first step toward treatment failure with this drug," Jambou says.



"When you use drugs in monotherapy, sooner or later you will develop drug resistance," says Pascal Ringwald of the World Health Organization. But he says the news comes several years sooner than most people expected.

Even so, Jambou says, if countries heed the early warning and crack down on unrestricted use of the drugs, there is a good chance they can preserve artemisinin's usefulness. He notes that it took 40 years for public health experts and governments to withdraw chloroquine from regular use after the first treatment failures: "If we use these compounds carefully, we still have time."

–G.V.

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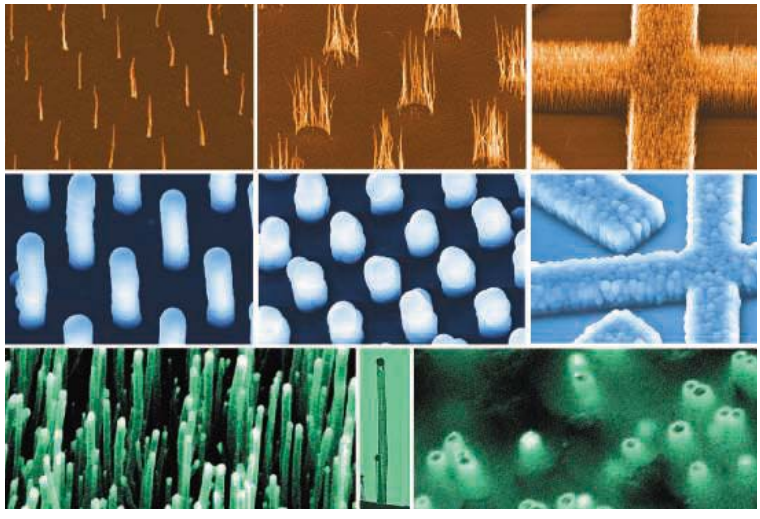
Calls Rise for More Research on Toxicology of Nanomaterials

Environmentalists and industry insiders alike urge major investments to maintain the emerging technology's spotless safety record

A rising chorus of government, industry, academic, and environmental leaders is calling for dramatic increases in funding to study possible adverse health and environmental effects of nanotechnology. These individuals—who don't often sing from the same songbook—argue that without this research, nanotechnology is setting itself up for the same kind of consumer backlash that has haunted genetically modified foods. In the past few weeks, the heads of DuPont and Environmental Defense and committees for the British Royal Society and the Science Council of Japan all have joined the choir.

Huge investments are at stake, they point out. The U.S. National Science Foundation projects that by 2015 nanotechnology will have a $1 trillion impact on the world economy and employ 2 million workers worldwide. Today, global spending on nanotechnology R&D is approximately $9 billion a year, about one-third of it in the United States. The U.S. federal government alone spends more than $1 billion a year on nanotechnology research. But only $39 million of that goes to studies targeted at understanding the effect of nanoparticles on human health and the environment. According to the Woodrow Wilson International Center for Scholars, which released an international database of nanotoxicology research projects last week, that still makes the United States the largest funder of nanotechnology environmental, health, and safety studies. The European Commission ranks second, with about $7.5 million.

Many experts now say that's not enough to test the hundreds of nanomaterials companies are pursuing. "Organizations as diverse as environmental NGOs [nongovernmental organizations], large chemical companies, nanotech start-ups, insurance companies, and investment firms all agree that the federal government should be immediately directing many more of the dollars it is currently investing in nanotechnology development toward identifying and assessing the potential risks of nanomaterials to human health and the environment," Richard Denison, a senior scientist with Environmental Defense in New York City, said last month in testimony before the United States House of Representatives Committee on Science. Denison and other nongovernmental witnesses at the hearing agreed that the United States should spend at least $100 million a year on testing how exposure to a wide array of nanoparticles affects cells and organisms. At the same hearing, Mathew Nordan, vice president of research for Lux Research Inc., a nanotechnology research firm, upped the ante: He suggested that governments worldwide devote as much as $200 million a year to a national nanotechnology toxicology initiative aimed at testing each of the myriad nanoparticles for threats to human and environmental health. "It only takes one bad apple to spoil the bunch," Nordan said.



CREDIT: NASA/AMES RESEARCH CENTER

Safe or sorry? Because a large percentage of their atoms lie on the surface, nanomaterials could be highly reactive—and potentially harmful.

Earlier this summer, DuPont CEO Chad Holliday and Environmental Defense's president Fred Krupp jointly penned an op-ed article in the *Wall Street Journal* arguing that nanotoxicity research should be boosted to 10% of the U.S. National Nanotechnology Initiative budget, up from the current level of about 4%. And a report published last week of a recent workshop organized by the United Kingdom's Royal Society and the Science Council of Japan said that "significant funding is urgently needed" for environmental, health, and safety studies of nanotechnology. On 30 November, after the U.K. government outlined a program to study the risks of nanotechnology, the Royal Society and the Royal Academy of Engineering called for earmarked funds to keep the initiative from turning into an ad hoc patchwork of research projects.

But with funding tight, says David Rajeski, who heads the Wilson Center's Project on Emerging Nanotechnologies, what's needed most is not more money but coordination. "We need an international nanorisk research program built on shared knowledge and a clear set of priorities," Rajeski says. As a possible first step, the Wilson Center recently compiled a database of more than 350 environmental health and safety studies in the United States, the United Kingdom, Canada, Germany, and Taiwan. Among the biggest gaps, it found, are studies of workplace safety issues, such as unintended worker exposure to nanoparticles from accidents.

Clayton Teague, who directs the U.S. National Nanotechnology Coordination Office, says that efforts are well under way to coordinate nanotoxicology research. In the United States, he says, a working group from 24 federal agencies is finishing a report that will set priorities for nanotoxicology research. And on the international front, progress could come as early as this week at a meeting of the Organisation for Economic Co-operation and Development in Washington, D.C. OECD member countries are considering setting up a permanent working group on establishing international nanotoxicology research priorities. Such measures, Teague and others argue, will better help governments decide just how much funding is needed for nanotoxicity research and ensure that it is money well spent.

Still, many toxicologists argue that commercialization of nanomaterials is rapidly overtaking efforts to study their impact on human and environmental health. "There has been a tremendous amount of discussion about increasing and coordinating nanotoxicology funding," says David Warheit, a nanotoxicology researcher at DuPont in Newark, Delaware. "But it's not happening as quickly as it should."

–ROBERT F. SERVICE

For Nuclear Fusion, Could Two Lasers Be Better Than One?

Whereas fusion energy from the sun is free, generating it on Earth costs. But laser researchers think they may have a budget route to boundless electricity

Doing nuclear fusion research usually means big bucks. The major industrialized nations are about to commit themselves to the $12 billion ITER fusion reactor project, the most expensive experiment ever, and both the United States and France are spending billions of dollars building the most powerful lasers in the world, in part to test another route to fusion. But another strategy has been developing quietly in the wings, one that uses two less powerful lasers instead of one big one. Advocates say that with a little encouragement, it could steal a march on the big facilities and carve a new, cheaper path to fusion.

All these approaches share a common principle: When hydrogen nuclei fuse to form helium, they release energy. But getting them to do so requires enormous temperatures and pressures, such as those in the core of the sun. The ITER reactor will use huge superconducting magnets to contain a hydrogen plasma and heat it enough for the nuclei to fuse. Designers are hoping it will produce more energy than is needed to run it.

But a subset of fusion researchers believe that the same result could be achieved using lasers rather than magnets to compress and ignite the hydrogen. The technique requires an enormous laser—the size of a sports stadium—to crush millimeter-sized capsules of hydrogen to 20 times the density of lead, inducing temperatures hotter than the core of the sun. Known as inertial confinement fusion, this technology is some years behind the ITER-style reactors. Researchers are pinning their hopes for a proof of feasibility on new machines such as the National Ignition Facility (NIF), now under construction at Lawrence Livermore National Laboratory in California, and the Laser Mégajoule (LMJ) being built by France's Atomic Energy Commission near Bordeaux.

But this strategy may be like lifting a sledgehammer to crack a nut, say advocates of fast-ignition laser fusion. Instead of using one very energetic laser to both compress the fuel and ignite it, fast ignition divides these tasks between two smaller lasers. The difference between the conventional single-laser method and fast ignition is akin to the difference between two types of internal combustion engines: In a diesel engine, a piston compresses the fuel-air mixture until it is hot enough to ignite spontaneously; whereas in a gasoline engine, the piston only compresses, and a spark plug lights the fuel. This division of labor in laser fusion relaxes certain requirements on the energy and uniformity of the compression stage. "It seems on paper that it is easier to use two lasers," says Riccardo Betti of the University of Rochester in New York.

Advocates of fast-ignition fusion have less experimental evidence to justify their optimism compared to rival technologies. An international team of researchers working in Japan has demonstrated that fast ignition can achieve fusion, but it is still a long way from showing it can achieve breakeven, the point at which the amount of energy produced equals what is put in. Efforts are under way in Japan and the United States to upgrade existing laser experiments for bigger tests of fast ignition, and European researchers have proposed a dedicated facility. Although uncertainties remain, fast ignition can potentially reach fusion with only a third of the compression used in conventional inertial confinement. "This translates into savings of a factor of 10 in the amount of energy needed to drive the compression," says Peter Norreys of the Central Laser Facility at Rutherford Appleton Laboratory in Didcot, U.K.

Laser Fusion Facilities

LASER FACILITY	LOCATION	COMPRESSION ENERGY	IGNITION POWER	ESTIMATED START
National Ignition Facility	United States	1.8 MJ	NA	2009
Laser MégaJoule	France	2.0 MJ	NA	2011
FIREX-I + Gekko XII	Japan	10 kJ	1 PW (10 kJ)	2007
OMEGA EP	United States	30 kJ	2 PW (5 kJ)	2007
HiPER	Europe	200 kJ	10 PW (70 kJ)	proposed

Division of labor

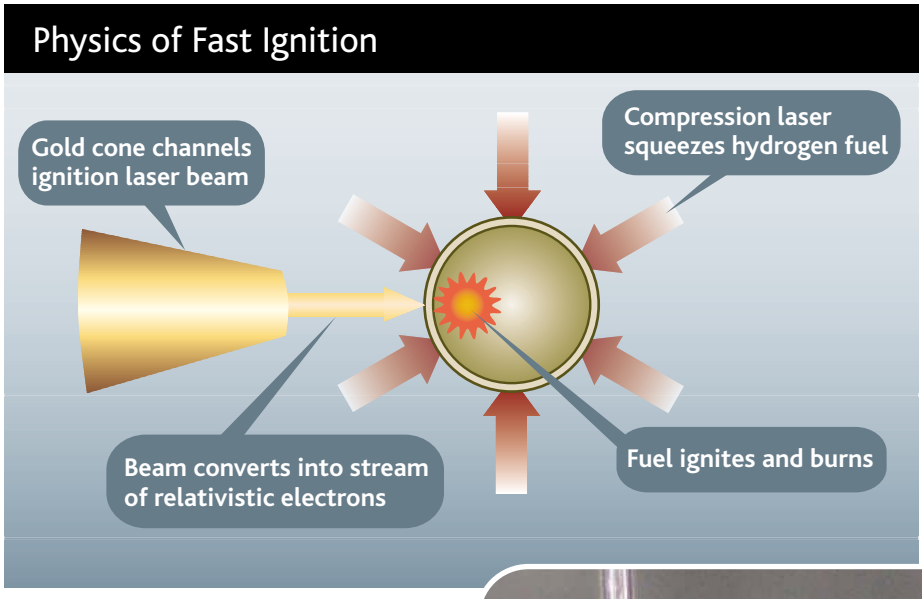
The basic objective is similar in both methods of laser fusion. Researchers focus light beams at a small, spherical shell containing the hydrogen isotopes deuterium and tritium. The intense heat causes the outer shell surface to rapidly boil off, and the material inside recoils and implodes. The huge pressure in the center then strips electrons off the hydrogen isotopes, creating the bugaboo of all fusion technologies: a highly ionized gas, or plasma. Plasmas are "notorious for having a host of instabilities" that can prevent a smooth burn, says Mike Dunne of the Rutherford Appleton Laboratory.

Thirty years ago, plasma physicists thought that a laser producing pulses with an energy of about a kilojoule (kJ) would be enough to collapse the hydrogen plasma and ignite fusion in the core. It wasn't. At high densities, they discovered, the plasma becomes unstable and the compression uneven. "The same kind of instability occurs in fluid dynamics, when a heavy liquid is supported by a lighter one," says Tito Mendonça of the Superior Technical Institute in Lisbon, Portugal. Cold material from the edges mixes into the core, effectively quenching the fire.

Researchers concluded that the way to get around this instability is to have a thicker shell around the fuel, but this also required lasers with much higher energies than were available at the time. This is where NIF and LMJ come in. Each of these billion-dollar projects, due for completion by the end of this decade, will provide roughly 2 megajoules (MJ) of laser energy. "My reading is that it is 90% certain they will get to ignition," Dunne says. The gain in energy is expected to be 10 to 20 times the energy supplied by the lasers. For actual energy production, however, gains would have to reach at least 100, because big lasers are currently very inefficient, Betti says.

Neither NIF nor LMJ can do fast-ignition studies now. They were built primarily with weapons research in mind and, by design, they use the conventional method because it mimics what happens in a hydrogen bomb. But there is talk of converting part of the laser capacity at NIF to short pulse, says Chris Barty of Lawrence Livermore. The primary motivation would be to create a "backlighter," a kind of high-speed camera to study the compression of targets. But the setup could be used for fast ignition as well. Currently, however, NIF has no funding for this retrofit, so researchers in this new field are making do with lasers

CREDIT: DATA PROVIDED BY MIKE DUNNE/HIPER PROPOSAL

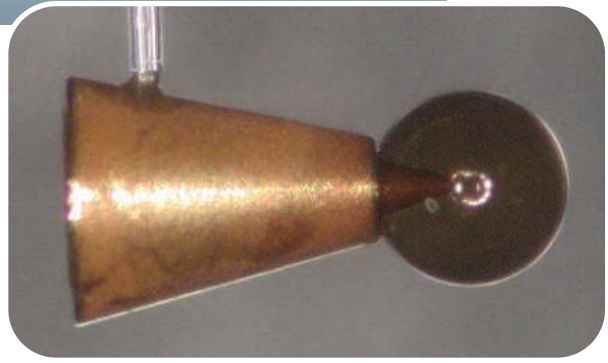


"Foolish" geometry. A gold cone is key in getting sufficient laser power into the capsule of hydrogen and igniting fusion.

at academic facilities with 1/100th the energy. "The good thing is that [fast ignition] has not been tremendously expensive up to now," says Max Tabak of Lawrence Livermore. "You can make progress with small teams."

Tabak, lead author of a 1994 paper that described a two-laser technique, is one of the pioneers of this cottage industry. The initial idea had been around for a few years, Tabak says, but he and his colleagues brought the pieces together for the first time. Early theoretical work showed that it would take a laser pulse of enormous power—but lasting a short time—to spark the plasma. This led to the development of the first petawatt (10^{15} watts) lasers in the 1990s. Although their power is equal to roughly 1000 times that flowing in the entire U.S. electricity grid, they deliver it in pulses of only a few tens of picoseconds (10^{-12} seconds), about a kilojoule each. If most of the pulsed energy penetrates the plasma and reaches the dense core, the fuel will ignite and burn.

The trouble is that when the laser light penetrates the plasma, it is converted into a beam of electrons that spreads out, lessening its power. Researchers came up with several ways to mitigate this beam spread. One favored new scenario is to insert a tiny hollow cone into the fuel capsule, a funnel-like short cut for the ignition energy so that the electron beam only has to travel a few tens of micrometers from the tip of the cone to the compressed core. There was initially a lot of skepticism that this "foolish geometry" would complicate the fuel assembly, recalls Ryosuke Kodama of Osaka University in Japan. However, using Osaka's Gekko XII laser facility, a collaboration of Japanese and British researchers led by Kodama in 2001 shot a 0.1-PW (60-J) pulse down the barrel of a gold cone, while a 1.2-kJ laser compressed the hydrogen fuel on the tip. The team observed a 10-fold—and later a 1000-fold—increase in the number of fusion-induced neutrons. "Gekko showed the possibility for fast heating in the imploded plasma," Kodama says. Although still far from the coveted ignition, this news made "a big splash," Tabak says.



Energy costs

The Gekko XII researchers estimated that about a quarter of the ignition laser's energy went into the fuel. This was a higher percentage than expected, according to Tabak. "Good things happened that we don't understand," he says. He is optimistic that the cone setup can be improved, but the next step will require more energy. U.S. researchers are in the process of adding a 2-PW (5-kJ) ignition laser to the 30-kJ OMEGA facility at the University of Rochester. Dubbed OMEGA EP, the experiment is expected to be ready in 2007. At Osaka University, a 1-PW (10-kJ) ignition laser, called FIREX-I, will complement the full compression laser (10 kJ) from Gekko XII in 2007. But beefing up the ignition energy could cause problems, Barty warns, as the laser-induced electron beam could shoot right past the core without sparking the fuel. "It's a concern," Norreys says, "but it's not a showstopper." There are ways essentially to slow the electron beam by shortening the wavelength of the infrared lasers.

Even so, Betti says these upgraded machines will probably not be powerful enough to reach fusion ignition. He estimates at least a 60-kJ compression laser is needed to achieve the breakeven point between energy in and out, and probably 700 kJ for a practical energy plant. The ignition laser may have much greater power, but its energy is lower, and energy is what costs money in the laser business, Dunne says.

In September, a panel of European scientists, including Dunne, presented a plan to really put the principle of fast ignition to the test. The panel wants European governments to build a civilian laser facility, called HiPER, with a 200-kJ compression laser and 10-PW (70-kJ) ignition laser, at a cost of $850 million. "This is a good time in Europe to start thinking about a facility," Betti says. Early results from FIREX-I and OMEGA EP could guide the development of HiPER's design. The proposal is currently being considered by the European Strategy Forum on Research Infrastructures, which is drawing up a road map of large science projects within the European Union.

The HiPER team hopes that building such a facility will free laser-fusion researchers from having to rely on military facilities. According to the panel, only about 15% of laser "shots" at NIF and LMJ will go to the academic community. Fast ignition offers the chance to achieve significant gains at a 10th of the energy needed for conventional inertial confinement. "Now there's a civilian route to the end point," Dunne says.

HiPER has another advantage, too: It can be used as a general laser facility for other branches of science, such as modeling stellar interiors and supernova explosions, studying nuclear interactions for medical imaging and waste management, and accelerating particles faster than current methods can. "There will be good science that comes out," Dunne says.

The lower price may also make fast ignition more practical as a possible source of energy. Researchers admit that fast ignition currently is not the favorite in the fusion race. But considering the need, "we should be working on anything that has a prayer," Tabak says.

–MICHAEL SCHIRBER

CREDITS: ADAPTED FROM UNIVERSITY OF ROCHESTER, LABORATORY FOR LASER ENERGETICS; (INSET) P. A. NORREYS *ET AL., PHYS. PLASMAS* 11, 2746 (2004)

Random Samples

Edited by Constance Holden

Ape Season Coming Up

Gigantopithecus, a huge ape that went extinct more than 200,000 years ago, is finally starring in its own documentary.

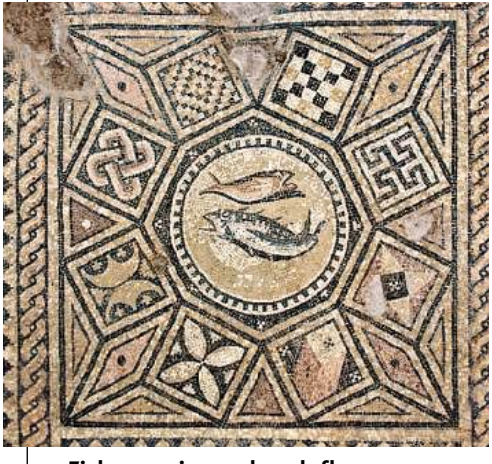
Anthropologist Russell Ciochon of the University of Iowa in Iowa City, who has studied fossils of the animal for 18 years, says he got backing from the History Channel to do a documentary because a new *King Kong* movie was in the works. "We're riding on the coattails," he says.

The male *Gigantopithecus* was more than twice the size of the largest known gorilla, weighing close to half a ton and standing more than 3 meters tall. The giant apes prowled the jungles of southern China and northern Vietnam during the Pleistocene, from about 2 million to 300,000 years ago, says Ciochon.

Giganto, as it is familiarly called, was first identified in 1935 when fossil collector Ralph von Koenigswald found a lower molar for sale as a "dragon's tooth" in a Chinese apothecary shop. Scientists have reconstructed the ape from three lower jaws and about 1000 teeth found at 10 cave sites. They postulated a skull scaled according to the dimensions of living apes and a body roughly 6.5 times the height of the skull.

Full-scale model of Giganto.

"Giganto, the Real King Kong," which features scientists from the Max Planck Institute for Evolutionary Anthropology in Leipzig and the Senckenburg Museum in Frankfurt, among others, includes views of cave sites in China, *Jurassic Park*–style animations of the animal, and a high-tech analysis of Giganto's teeth. It will be aired on the History Channel on 15 December, the day after the new *King Kong* movie debuts.



Fish mosaic on church floor.

Earliest Church

A team of archaeologists last month announced discovery of the remains of a 3rd century church in Israel, possibly the oldest Christian church in the Holy Land.

The find was made by chance in October by prisoners working on the construction of a new prison in what was once the ancient Roman-Byzantine village of Kefar Otnai, near the biblical Armageddon. Archaeologists subsequently uncovered an elaborate mosaic floor bearing two inscriptions in ancient Greek, geometric patterns, and fish, a Christian symbol predating the cross. Yotam Tepper of the Israel Antiquities Authority says one inscription reveals that a Roman military officer donated money to build the mosaic; the other mentions that a woman donated the table used as an altar in memory of "the god, Jesus Christ."

The remains, dated through pottery shards at the site, are "very important to the study of early Christianity in the Holy Land," because they reflect a time when Christians were still worshipping in secret, says anthropologist Joe Zias of the Hebrew University of Jerusalem. If the dating is correct, the inscription mentioning the Roman soldier is "perplexing," notes Zias, because Christianity was not fully recognized by the Roman Empire until the Edict of Milan in 313 C.E.

Sign of the Times

Soaring obesity rates may make it increasingly tough for doctors to give patients their best shot: Standard needles aren't long enough to deliver intramuscular injections to many buttocks, according to researchers at a hospital in Dublin, Ireland. A study of 50 patients found that in two-thirds of them—including almost all the women—the drugs were getting stalled in fat tissue, the researchers said last week at the Chicago meeting of the Radiological Society of North America.

Physics Society Decides To Stay Physical

After much deliberation, the American Physical Society (APS) has decided not to change two letters in its name. The society's executive board had been considering changing "physical" to "physics" to avoid confusion with gym teachers and physical therapists. In an e-mail survey of members this summer, 75% of respondents favored the change.

But "we probably should have gone to our lawyers before going to our members," says APS official Alan Chodos. Last month, the executive board decided the change would cause too many legal headaches: The society would have to reincorporate and might have to renegotiate contracts. The board opted instead to add "physics" to the APS logo. "The name stays as it was," says APS president Marvin Cohen, but "you're not going to see it anymore."

CREDITS (TOP TO BOTTOM): RUSSELL CIOCHON/RECONSTRUCTION BY BILL MUNNS; YOTAM TEPPER

Edited by Yudhijit Bhattacharjee

MOVERS

Universal language. After decades of climbing the academic ladder, chemist Suzanne Fortier took a sabbatical this year from Queen's University in Ontario, Canada, to learn Italian at the University of Bologna. But next month, those studies will have to end so that she can run Canada's Natural Sciences and Engineering Research Council (NSERC). The 56-year-old Fortier succeeds Thomas Brzustowski, who is leaving after two 5-year terms as head of the $600-million-a-year granting agency.

Fortier was the vice president of the council from 1997 to 2002, and she's not planning to make significant changes to the current array of NSERC programs. But she hopes to foster more collaborations among researchers and institutions. "We have to work together if we want to be significant players on the world stage."

She also wants to cut red tape. "By doing all we can to be efficient and responsive, [I hope to] facilitate the work of our researchers."

AWARDS

Shining early. Mathematicians are said to do their best work when young. That's the logic behind the age-40 ceiling for the Fields Medal, the Nobel equivalent for mathematicians. Now Shanmugha Arts, Science, Technology, and Research Academy (SASTRA) University in Kumbakonam, India, has moved the clock forward, instituting an annual $10,000 Ramanujan Prize for those 32 or under. Srinivasa Ramanujan grew up in Kumbakonam and died in 1920 at 32.

Both the inaugural recipients happen to be of Indian heritage: Manjul Bhargava (right), 30, of Princeton University, and Kannan Soundararajan (left), 31, of the University of Michigan, Ann Arbor. The pair is cited for pioneering work in number theory: Bhargava for composition laws in the arithmetic of algebraic number fields and Soundararajan for the Riemann zeta function and related problems in analytic number theory. They will receive the prize in Kumbakonam on 22 December, Ramanujan's birthday.

POLITICS

Fished out. Fisheries biologist Michele DeHart thought she was just doing her job when her Fish Passage Center came out in support of a federal court's ruling to help salmon by spilling extra water from dams on the Snake River. But her memo last summer so rankled Senator Larry Craig (R–ID) that he persuaded Congress last month to yank the $1.1 million in federal funding that supports the 12-person agency.

The Portland, Oregon–based center has been monitoring salmon health in the Pacific Northwest region for 22 years. DeHart, 55, says she's "really got a problem" with Craig's statement on the Senate floor last month that suggested the center's data was tainted by advocacy. "Sometimes in resource management you might not like the way the data turn out," says DeHart. "But that really falls into killing the messenger."

Dan Whiting, a spokesperson for Craig, says his boss thinks the center crossed the line with its memo regarding a court order that will cost utility companies millions of dollars. "There's a difference between data collection and advocacy," Whiting says.

But DeHart contends that the memo's language is simply factual and is based on objective data and analysis. And after all, she says, "it's generally a good idea to implement a court order. I've been just shocked and surprised that this kind of thing actually does happen in the legislative process."

THEY SAID IT

"[John F. Kennedy] didn't know a gene from a chromosome, ... [but] he wanted to know all the facts. It was a golden age for science."

—Theodore Sorensen, a longtime aide to the Democratic president, speaking last week at the 60th anniversary of the Federation of American Scientists. He was comparing attitudes toward science in the Kennedy Administration and in the current White House.

IN THE NEWS

Of pandas and people. Reproductive biologist Jo Gayle Howard of the Smithsonian's National Zoo was as proud as any parent would be when Tai Shan, the zoo's 5-month-old panda cub, met the media last week. Howard oversaw panda mom Mei Xiang's artificial insemination, a tricky procedure because of the slim 24- to 48-hour ovulation window. But her work and Mei Xiang's dedication have produced a healthy 10-kg cub, the first to survive past 3 days at the Washington, D.C., zoo.

Got any tips for this page?
E-mail people@aaas.org

CREDITS (TOP TO BOTTOM): DENISE APPLEWHITE/PRINCETON UNIVERSITY OFFICE OF COMMUNICATIONS; UNIVERSITY OF MICHIGAN PHOTO SERVICES; NSERC; JESSIE COHEN/SMITHSONIAN'S NATIONAL ZOO

ScienceCareers.org is the leading careers resource for scientists. And now it offers even more. In addition to a brand new website with easier navigation, ScienceCareers.org now includes Next Wave, the essential online careers magazine. Next Wave is packed with features and articles to help advance your science career – all for free.

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Support for the Human Cancer Genome Project

IN "AN OPEN LETTER TO CANCER RESEARCHERS" (Letters, 21 Oct., p. 439), S. J. Elledge and G. J. Hannon questioned the wisdom of asking the NIH to undertake the Human Cancer Genome Project (HCGP) (*1*) recently proposed by a National Cancer Institute Working Group, of which we were members. Elledge and Hannon object to the HCGP on the grounds that the project is unlikely to achieve its goals, that the expenditures would decrease funding available for investigator-initiated projects, and that the funds could be better used to support other work, such as genetic screens for factors required for the growth and survival of cancer cells.

Although we welcome debate about the Working Group's proposal and do not dispute the value of genetic screens, the Letter misrepresents the HCGP. First, it undervalues the goal of the project, which is to provide as thorough an account as currently possible, now that the human genome has been sequenced, of the genetic damage responsible for many different types of human cancer. Second, it fails to describe the systematic and progressive aspects of the plan: to begin with pilot projects and to link clinical information about tumor samples to the underlying genetic changes in cancer cell DNA. The proposal limits resequencing to the coding exons of 1000 to 2000 genes, not entire genomes, and suggests that genes with altered copy number changes be given some priority (*1*). Third, Elledge and Hannon greatly underestimate the evidence that already supports the utility of such genotyping, including the many changes in proto-oncogenes and tumor suppressor genes that are already affecting the approaches to diagnosis, classification, and treatment of these diseases (*1*). Finally, the Letter fails to recognize a crucial implication of three recent studies that the authors cite in support of their opposition to the HCGP (*2*–*4*). In each of these three studies, it is apparent that a systematic study of larger numbers of well-defined tumor types and candidate genes, exactly the strategy embraced by the HCGP, will be required to identify the genetic damage that underlies these cancers. In fact, in two of the papers cited (*3*, *4*), because so few tumors from each of the specific histological types were examined, well-validated classes of mutations—*EGFR* mutations in lung adenocarcinomas and *KIT* mutations in seminomas—were not found.

Techniques for detection of some genetic changes are ready for systematic linking to clinical data. We recognize that resequencing is still difficult and expensive, that costs may decline in the future if we wait for methods to improve, and that tests for chromosomal translocations and epigenetic changes may not yet be ready for high-throughput use. Furthermore, budget projections for the NIH imply that the costs of the HCGP will require some reductions in other activities. Nevertheless, we contend that the cancer research community now needs a much better description of the genetic damage that drives human cancers; this will form the basis for all future studies of cancer in the laboratory and the clinic and will provide immediate benefit for molecular diagnosis of human cancers.

The National Cancer Institute and the National Human Genome Research Institute have recently endorsed the idea of conducting pilot projects to compare existing methods for characterizing cancer genomes, to evaluate the feasibility of resequencing genes on the scale proposed, and to examine the potential for discovery. We think that these are responsible first steps toward the goals of the HCGP.

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> "[W]e contend that the cancer research community now needs a much better description of the genetic damage that drives human cancers; this will form the basis for all future studies of cancer in the laboratory and the clinic and will provide immediate benefit for molecular diagnosis of human cancers."
>
> –VARMUS AND STILLMAN

Attribution of Disaster Losses

IN HIS VIEWPOINT "INSURANCE IN A CLIMATE OF change" (12 Aug., p. 1040), E. Mills suggests that changes in climate have been responsible for some part of the trend in recent decades of increasing damage related to extreme weather. This claim is not supported by the peer-reviewed literature, including the most recent report of the Intergovernmental Panel on Climate Change (IPCC) (*1*).

Over recent decades, the IPCC found no long-term global trends in extratropical cyclones (i.e., hurricanes or winter storms), in "droughts or wet spells," or in "tornados, hail, and other severe weather" (*2*). Logically, in the absence of trends in these weather events, they cannot be responsible for any part of the growing economic toll. The IPCC did find "a widespread increase in heavy and extreme precipitation events in regions where total precipitation has increased, e.g., the mid- and high latitudes of the Northern Hemisphere" (*3*). But at the same time, the IPCC warned that "an increase (or decrease) in heavy precipitation events may not necessarily translate into annual peak (or low) river levels" (*3*). Indeed, although the IPCC found some changes in streamflow, it did not identify changes in streamflow extremes (i.e., floods) and concluded on a regional basis, "Even if a trend is identified, it may be difficult to attribute it to global warming because of other changes that are continuing in a catchment" (*4*). These findings are consistent with research seeking to document a climate signal in a long-term record of flood damage that has concluded that an increase in precipitation contributes to increasing flood damage, but the precise amount of this increase is small and difficult to identify in the context of the much larger effects of policy and the ever-growing societal vulnerability to flood damage (*5*, *6*). A recent study by the International Ad Hoc Detection and Attribution Group concluded that it was unable to detect an anthropogenic signal in global precipitation (*7*).

Presently, there is simply no scientific basis for claims that the escalating cost of disasters is the result of anything other than increasing societal vulnerability (*8*).

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3. See section 2.7.2.2 of (*1*) at www.grida.no/climate/ipcc_tar/wg1/090.htm.
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Response

WHILE WORTHY OF DISCUSSION, THE HISTORically oriented questions raised by Pielke Jr. are tangential to the central focus of my Viewpoint, which explores the vulnerability of insurers, their customers, and governments to future climate change.

Climate change cannot be summarily dismissed as a driver of observed growth in global weather-related damages and economic losses. The disaster attribution literature upon which such assertions are based is fraught with data and measurement uncertainties and is decidedly incomplete, especially concerning events outside the United States (*1*). There is particularly scant treatment of important noncatastrophic processes such as small storms, lightning, soil subsidence, permafrost melt, the effects of mold and airborne aeroallergens on human health, coral reef decline, coastal erosion, or crop diseases. Such diffuse or small-scale phenomena today yield aggregate annual losses on a par with headline-catching catastrophes and will be amplified by climate change (*2*, *3*). Indirect effects, such as impacts on energy prices, are significant but rarely quantified.

Damage to oil storage tanks in Cameron, Louisiana, caused by Hurricane Rita.

A nonselective reading of IPCC's 2001 assessment does in fact support the linkage between rising damage costs and a combination of increased weather extremes and societal vulnerability. This is stated directly in the WG2 Technical Summary and elsewhere. IPCC's synthesis of the literature notes observed underlying changes in temperature and precipitation extremes, continental drying, and a range of associated impacts on physical and biological systems. Moreover, the body of literature demonstrating anthropogenic climate change has since bourgeoned, evidencing stronger and more pervasive trends (*1*, *4*) including changes in atmospheric and ocean circulation and elevated ocean heat content, as well as sea-level rise and associated coastal erosion, which, in turn, help drive many impacts of concern (*5*, *6*). The recent literature on the socially and economically devastating European heat wave of 2003 attributes a very high (90%) confidence that human activity doubled the probability of the event's occurrence (*7*).

It is clear that global economic losses from weather-related events are rising far faster than inflation, economic growth, or population. Thorough attribution analysis must address questions such as:

Why are losses from weather-related events rising faster than those from non-weather events?

What are the offsetting effects of human efforts to curb losses (building codes, early warning systems, fire protection, flood defenses, land-use planning, crop irrigation, etc.)? As noted by Pielke Jr. and co-authors with respect to flood risk [(*8*), p. 1081], "[o]ne can easily hypothesize that increasing population and urbanization in the United States has led to a commensurate increase in population at risk. Yet, one can also hypothesize that the various societal responses may have more than compensated for population growth and in fact fewer people are today at risk...." The Army Corps of Engineers estimates that flood control measures have prevented 80% of U.S. losses that would have otherwise materialized (*9*).

How do we explain rising economic losses (e.g., those to crops in the heartland or physical infrastructure built on melting permafrost) that are only weakly linked to oft-cited demographic factors such as populations clustering around coastlines?

Lastly, why would rising numbers of events (*10*) not translate into rising costs?

Assuming that only socioeconomic factors—rather than rising emissions—influence losses may yield ill-founded policy recommendations that focus exclusively on adapting to climate change while dismissing energy policy as a legitimate part of the toolkit for responding (*11*). As an indication of the potential value of emissions reductions, the Association of British Insurers, in collaboration with U.S. catastrophe modelers, estimated that U.S. hurricane or Japanese typhoon losses would vary by a factor of five for scenarios of 40% and 116% increase in pre-industrial atmospheric CO_2 concentrations (*12*). Others have projected a fourfold increase in mid-Atlantic U.S. flood loss costs under climate change (*13*).

In a narrow sense, it would be a relief to learn that the only cause of rising losses is that people are moving more into harm's way. That conclusion would, however, be premature and scientifically indefensible given the paucity of data, limitations of available analyses, and consistency between observed impacts and those expected under climate change. Nor should we make the opposite mistake of attributing the observed growth in losses solely to climate change. Rather than "proof" by vigorous assertion, the constructive approach is to better understand the compounding roles of increasing vulnerability and climate change, and take affordable precautionary steps to reduce greenhouse gas emissions and adapt to the changes rather than waiting for unaffordable consequences.

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Bilateral Action for Right Whales

IN THEIR POLICY FORUM "NORTH ATLANTIC right whales in crisis" (22 July, p. 561), S. D. Kraus *et al.* make clear the plight of the North Atlantic right whale, *Eubalaena glacialis*, and note that whale deaths from ship strikes and fishing gear entanglements have not been diminishing. Kraus *et al.* call for changes to U.S. National Oceanic and Atmospheric Administration (NOAA) management policy to put strong and immediate

CREDIT: TIM JOHNSON/REUTERS

emphasis on reducing human-induced mortality of right whales. The species, though, is not restricted to U.S. waters; it ranges from Florida to the Canadian Maritimes. It is listed as Endangered under both the U.S. Endangered Species Act and the Canadian Species at Risk Act.

CREDIT: NOAA

U.S. and Canadian protection and recovery policies for North Atlantic right whales, administered respectively by NOAA and Fisheries and Oceans Canada (DFO), are not precisely the same. Although the current U.S. and Canadian plans both make reducing mortality due to ship strike and net entrapment a higher priority than reducing habitat degradation, the Canadian plan does not address direct human lethal take (*1*, *2*). Bilaterally agreed-upon management policy is essential for the protection of globally endangered migratory species that cross political boundaries. A precedent was set by the bilateral recovery efforts in aid of the whooping crane. Some level of cooperation between the two countries has been achieved regarding the right whale, but it is insufficient to call only for changes to NOAA management policy when coordinated, bilateral management; regular joint meetings; and cooperative actions are needed. The new U.S. recovery plan calls for bilateral cooperative efforts to maximize protection for right whales. Canadian recovery planning should follow suit and both jurisdictions should work together.

JESSE S. SAYLES AND DAVID M. GREEN

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Response

WE AGREE WITH SAYLES AND GREEN. Migratory transboundary species like the right whale require bilateral efforts at many levels. For example, the U.S. National Marine Fisheries Services' Advanced Notice of Proposed Rulemaking (*1*) does require the U.S. government to work with Canada to develop bilateral agreements related to shipping. Further, most co-authors on the Policy Forum have benefited from close working relationships with both researchers and managers within Fisheries and Oceans Canada (DFO).

Several breakthroughs in right whale conservation have already been made in Canada, including relocation of the internationally adopted shipping lanes in the Bay of Fundy to reduce ship kills, as well as the official recognition of two Conservation Areas where right whales aggregate. The Bay of Fundy shipping lane changes resulted from efforts by Irving Oil, Transport Canada, DFO, the International Maritime Organization, fishing organizations, whale watching groups, and right whale conservationists. Such multilateral partnerships are especially important in conserving transboundary species.

However, we are aware that DFO's ability to really make a difference to right whale conservation is dependent on funding for their initiatives, and support for recovery plan implementation has been limited. We encourage both the Canadian government and nongovernmental organizations to support increased funding for right whale conservation in Canada and welcome additional collaboration with our Canadian colleagues, particularly in the development

of bilateral measures to ensure the protection of right whales throughout their range.

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CORRECTIONS AND CLARIFICATIONS

Reports: "Air-stable all-inorganic nanocrystal solar cells processed from solution" by I. Gur *et al.* (21 Oct., p. 462). On page 464, in two places, it is mentioned that an aging experiment was carried out for 13,000 hours. These instances should read ~13,000 minutes. These errors occur in line 4 of the Fig. 4 caption and in column 2, fourth paragraph, line 8.

TECHNICAL COMMENT ABSTRACTS

COMMENT ON "How Science Survived: Medieval Manuscripts' 'Demography' and Classic Texts' Extinction"

Georges Declercq

Exciting though it may seem, the mathematical model developed by Cisne (Reports, 25 February 2005, p. 1305) to analyze the transmission of texts and manuscripts from Antiquity and the Middle Ages does not hold up to scrutiny. It seriously underestimates the losses, thus leading to conclusions that are unwarranted.

Full text at www.sciencemag.org/cgi/content/full/310/5754/1618b

RESPONSE TO COMMENT ON "How Science Survived: Medieval Manuscripts' 'Demography' and Classic Texts' Extinction"

John L. Cisne

Declercq's rejection of an otherwise well-supported model is based on demonstrably too narrow an interpretation of the use of Bede's *De Temporum Ratione* and on questionable appreciation of predictive modeling as a complementary alternative to traditional deductive methods. Additional evidence on library holdings further supports the original conclusions regarding the survival of manuscripts.

Full text at www.sciencemag.org/cgi/content/full/310/5754/1618c

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 6 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

EVOLUTION

On the Origins of Novelty and Variation

Brian Charlesworth

In chapter 6 of *The Origin of Species*, Charles Darwin confronted the problem of explaining the evolution of complex pieces of biological machinery. How can natural selection, acting on "random" variation, produce a beautifully functioning structure made up of many integrated components, such as the vertebrate eye? His answer was that a structure like an eye is built up by a process of stepwise change from a primitive ancestral state, such as a simple group of light-receptive cells, leading eventually to the complicated vertebrate system of lens, iris, retina, optic nerve, etc. Each successive elaboration increases the efficiency of an already serviceable organ. Many such steps collectively produce a combination of characters that could never have existed in the ancestor. Although in the majority of cases we have no direct information on the steps that actually occurred in the evolution of complex adaptations, there are many examples of intermediate states that can be observed in living forms, as is indeed the case for the eye. The consensus among evolutionary biologists is that Darwin's interpretation has successfully stood the test of time, although the news has apparently not reached Kansas.

The Plausibility of Life
Resolving Darwin's Dilemma
by Marc W. Kirschner and John C. Gerhart

Yale University Press, New Haven, CT, 2005. 330 pp. $30, £18.95. ISBN 0-300-10865-6.

In *The Plausibility of Life*, an account intended for a general readership, Marc Kirschner and John Gerhart argue that the Darwinian explanation is incomplete and that the results of recent discoveries in cell and developmental biology can be used to remedy this defect. Are they right, or does their effort represent the latest entry in the catalogue of failed attempts by developmental biologists to supplement or replace neo-Darwinian evolutionary biology?

Unlike some of their predecessors, Kirschner (the chair of Harvard's Department of Systems Biology) and Gerhart (a professor in Berkeley's Department of Molecular and Cell Biology) are not hostile to the view that evolutionary change at the level of morphology or behavior is the product of natural selection acting on variation that arises ultimately from mutation. Rather, they argue that the basic properties of cells and their interactions during development have profound consequences for the properties of the variability available for use by selection. These properties and interactions both constrain the possible types of alteration to the organism's structures and offer opportunities for the rapid evolution of novel structures. The authors call the latter "facilitated variation," which they define as:

> An explanation of the organism's generation of complex phenotypic change from a small number of random changes of the genotype. We posit that the conserved components greatly facilitate evolutionary change by reducing the amount of genetic change required to generate phenotypic novelty, principally through their reuse in new combinations and in different parts of their adaptive ranges of performance.

Kirschner and Gerhart point out that development in multicellular animals is controlled by signal-response systems, in which many of the individual components are highly conserved over much of metazoan evolutionary history. The same molecules are often reused in different contexts; this "weak linkage" between signal and response permits conserved components to be combined in different contexts, allowing a novel outcome of development to be produced without the invention of new individual components. The authors also emphasize the flexibility of developmental systems, so that a change in the shape of a bone, for example, induces corresponding changes in the placement of blood vessels, nerves, etc., without requiring additional genetic changes. These points are illustrated with many impressive examples drawn from developmental and cell biology, subjects that are far better understood than when the modern synthesis of evolutionary biology was developed during the 1930s to 1950s. Perhaps the most striking example is the conservation of the basic genetic circuits underlying the body plans of animals as distant as vertebrates and arthropods, a great advance in our knowledge of the history of life.

The question is whether this adds substantially to our understanding of the causal processes of evolution. The authors' picture of the modern synthesis is rather a caricature. Early in their chapter on the sources of variation, they state "There are limits on what selection can accomplish. We must remember that it merely acts as a sieve, preserving some variants and rejecting others; it does not create variation. If genetic change were random, what could ensure that enough favorable phenotypic variation had taken place for selection to have produced the exquisite adaptations and variety we see on the earth today?" Near its end, they wonder "What if evolutionary biologists were wrong to think of phenotypic variation as random and unconstrained, even though genetic variation was random and unconstrained?"

There seem to be two mistakes here. First, the view of selection as a sieve ignores its ability to produce new combinations of characters, mentioned earlier. Such combinations give selection a truly creative aspect, as was strongly emphasized by Darwin himself and by many founders of the modern synthesis, whereas Kirschner and Gerhart focus on single mutational events. Second, the synthesis's founders were well aware of the fact that mutational effects are not unconstrained. For example, in 1947 H. J. Muller wrote that "the organism cannot be considered as infinitely plastic, and certainly not as equally plastic in all directions, since the directions which the effects of mutations can take are, of course, conditioned by the entire developmental and physiological systems arising from the action of all the other genes already present" (*1*).

Evidence of evolution's inventive powers.

It is very difficult, even now, to determine the potential range of variability in a given character, other than by examining the variability either produced by new mutations or present in natural populations. That is, of course, precisely what is done by evolutionary biologists interested in a particular trait. Until we have a predictive theory of developmental genetics, our understanding of the molecular basis of development—however fascinating and important in revealing the hidden history of what has happened in evolution—sheds lit-

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tle light on what variation is potentially available for the use of selection. As a result, it is currently impossible to evaluate the idea that developmental systems have special properties that facilitate variation useful for evolution. Indeed, Kirschner and Gerhart do not present any detailed examples of how the properties of developmental systems have actually contributed to the evolution of a major evolutionary novelty. Nor have they shown that alternative properties would have prevented such evolution. Although *The Plausibility of Life* contains many interesting facts and arguments, its major thesis is only weakly supported by the evidence.

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PHYSICS

Many Perspectives on Swinging

Alberto G. Rojo

In 1911, at the first Solvay Conference in Brussels, Albert Einstein and Hendrik A. Lorentz discussed a simple problem that later led to a central research tool within what we now call the "old quantum theory." At the time, it was assumed that mechanical systems subject to the yet embryonic quantum laws could only make "all or nothing jumps" between allowed states of different energy. What would happen, Lorentz asked, if one takes a pendulum with an allowed energy and shortens the length of the string by grasping it with two fingers? Einstein remarked that, even though the pendulum's period would decrease and its energy would increase, if the string is shortened very slowly ("adiabatically"), the product of the two quantities will remain constant: a pendulum whose frequency changes adiabatically does not undergo a quantum jump and the product of the period and frequency is quantized.

This episode is just one of many notable instances in which the pendulum, the most famous of mechanical systems, surfaces in the history of physics. Our world abounds with examples of cyclic motions whose mathematical description is the same as that of the pendulum or coupled pendulums: Sound waves of well-defined frequency are oscillations of air pressure and velocity exactly analogous to the velocity of a pendulum at small displacements from its equilibrium position. Coupled microscopic magnets in a solid act as coupled pendulums and give rise to oscillations called magnons. Neutrino oscillations can be described as two coupled pendulums. And when humans walk, they do so as inverted pendulums. Given the ubiquity of this kind of periodic motions in physics, a book devoted thematically to the history and physics of the pendulum is most welcome.

The Pendulum
A Case Study in Physics
by Gregory L. Baker and James A. Blackburn
Oxford University Press, Oxford, 2005. 300 pp. $89.50, £45. ISBN 0-19-856754-5.

In *The Pendulum: A Case Study in Physics*, Gregory Baker and James Blackburn do an excellent job of weaving physical explanations with literary quotes and amusing anecdotes from the history of science. The authors are physicists who teach at Bryn Athyn College, Pennsylvania, and Wilfred Laurier University, Ontario, respectively, and they have written their account for undergraduate physics majors. After presenting simple examples of the linearized pendulum, the discussion turns to the nonlinear pendulum and parametric amplification with nice (although not fully self-contained) treatments of the pumping of a swing and O Botafumeiro, a giant censer at the cathedral of Santiago de Compostela in northwest Spain. (A team of men pull the supporting rope in a pumping cycle, thus transforming the censer's motion into that of a variable-length pendulum and increasing the system's energy and angle of oscillation.) A chapter devoted to the Foucault pendulum (which demonstrates Earth's rotation) combines the historical narration with a full treatment of the physical problem. The consideration of the torsion pendulum focuses on Henry Cavendish's 1798 experiment to measure the Newtonian gravitational constant G and Roland von Eötvös's results that established the equivalence of gravitational and inertial mass. The authors' presentation of the chaotic pendulum includes a good introduction to Poincaré sections and Lyapunov exponents.

The chapter on coupled pendulums could be used to introduce students to the physics of synchronization, a phenomenon that, as the authors explain, dates back to Christiaan Huygens and his observation of the synchronization of clocks hanging from the walls in his workshop. Baker and Blackburn offer a rather standard textbook treatment of the quantum mechanical harmonic oscillator and the Mathieu equation that describes the quantum mechanical simple pendulum. They next discuss superconductivity from the point of view of the macroscopic wave function and present Feynman's treatment of the Josephson junction using the algebra of coupled pendulums. The book culminates with an appealing treatment of the pendulum clock and Huygens's *Horologium Oscillatorium*, which includes a discussion of the escape mechanism in pendulum clocks, a topic not usually found in physics texts.

The book offers a tour of different incarnations of the pendulum, with nice interludes on Edgar Allan Poe's "The Pit and the Pendulum" (they don't reveal the end of the story) and "His Burial Too," Catherine Aird's mystery in which Foucault's pendulum is used as a murder weapon. In places, the mathematical treatments are incomplete and refer the reader to advanced texts. (Such is the case for the consideration of parametric forcing, which starts from the Lagrange formalism.) Although the book contains a good collection of end-of-chapter problems, it stands roughly midway between a monograph and an overview—with a slight emphasis on the encyclopedic rather than on new physical insights into well-known problems. As Baker and Blackburn state in the preface, *The Pendulum* is an unusual book. An enjoyable theme and variations, it is well suited for use as a resource or as a recommended text in an advanced course on mechanics.

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The philosopher and the pendulum. Engraving from *L'Illustration* (Paris, 1851).

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AGRICULTURE

Losing the Links Between Livestock and Land

Rosamond Naylor,[1,2]* Henning Steinfeld,[4] Walter Falcon,[2] James Galloway,[5] Vaclav Smil,[6] Eric Bradford,[7] Jackie Alder,[8] Harold Mooney[3]

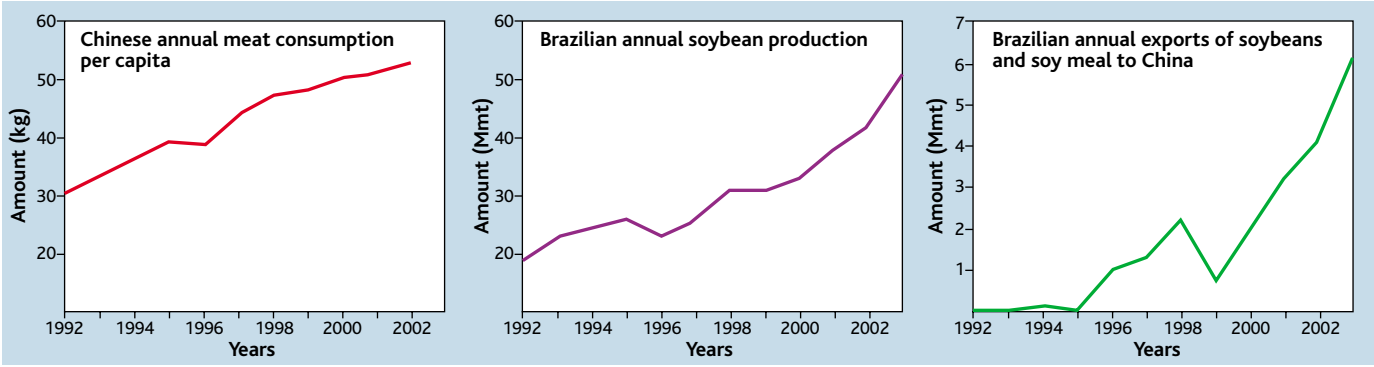
The industrial livestock sector has become footloose—no longer tied to a local land base for feed inputs or to supply animal power or manure for crop production. Spatially clustered within and among countries, this sector is expected to meet most of the income-driven doubling in meat demand forecast for developing countries by 2030 (*1*). Large-scale, intensive operations, in which animals are raised in confinement, already account for three-quarters of the world's poultry supply, 40% of its pork, and over two-thirds of all eggs (*2*). International trade in meat is also expanding; during the past 15 years, annual trade volumes have increased by 5.5% for pork and 8% for poultry (*3*). Livestock remains the world's largest user of land, but its use has shifted steadily from grazing to the consumption of feed crops. Unfortunately, environmental and resource costs of feed-crop and industrial-livestock systems—often separated in space from each other and from the consumer base—remain largely unaccounted for in the growth process.

Industrializing and globalizing livestock systems have hinged on declining real prices for feed grains; advances that have improved feed-to-meat conversion efficiencies, animal health, and reproduction rates; relatively cheap transportation costs; and trade liberalization. The most dramatic shift has been toward the production of monogastric animals, such as chickens and hogs, which use concentrated feeds more efficiently than cattle (or sheep) and which have short life cycles that accelerate genetic improvements. The average time needed to produce a broiler in the United States was cut from 72 days in 1960 to 48 days in 1995, and the slaughter weight rose from 1.8 to 2.2 kg (*4*). Meanwhile, feed conversion ratios (FCR, kg feed per kg meat) were reduced by 15% for broilers and over 30% for eggs (*5*). Annual growth in hog and poultry production in developing countries was twice the world average in the 1990s (*2*). By 2001, three countries—China, Thailand, and Vietnam—accounted for more than half the hogs and one-third the chickens produced worldwide (*1*). Brazil is also a major producer and is expected to become the world's leading meat exporter.

Virtually all of the growth in livestock production is occurring in industrial systems—a trend that has been evident in the United States for several decades. Industrial poultry and pork operations are largely uniform worldwide, which facilitates a rapid transfer of breeding and feeding innovations. Larger firms typically control production from animal reproduction to the final product, mainly to minimize economic and pathogen risks. As these firms increasingly supply major retail chains, corporate attention is directed toward food safety and the production of homogeneous (yet diverse), high-quality products. In addition to scale, industrial livestock operations have become concentrated geographically in areas where input costs are relatively low; infrastructure and access to markets are well developed; and in many cases, environmental regulations are lenient (*6*).

The most striking feature of this geographic concentration is the delinking of livestock from the supporting natural resource base. Feed is sourced on a least-cost basis from international markets, and the composition of feed is moving up the chain from agricultural by-products to grain, oil-meal, and fish-meal products that have higher nutritional and commercial value. Although FCRs for chickens and hogs on an edible weight basis are roughly one-fifth and one-third, respectively, that of cattle (whose diets include rangeland forage, crop residues, and by-products) (*7*), monogastric diets are richer in cereal and legume feeds, which compete with food crops for land and water.

Future land needs for industrial livestock production are potentially great. For example, a balanced Chinese diet of the early 1990s containing 20 kg meat per capita per year was produced from an average land area of just over 1000 m^2/capita, whereas a typical Western diet required up to four times that area (*7*). China's meat consumption, consisting mainly of pork, is increasing rapidly with income growth and



International linkages in supply and demand of livestock products, 1992–2003 (*3*). Mmt, millions of metric tons.

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urbanization; it has more than doubled during the past generation (*3*). If the world's population today were to eat a Western diet of roughly 80 kg meat per capita per year, the global agricultural land required for production would be about 2.5 billion hectares—two-thirds more than is presently used (*4*). Continued crop intensification could offset some of this land requirement, but would also have consequences for water use and nutrient pollution even if precision agriculture were widely practiced.

Land conversion in the Brazilian *cerrado* (grassland) and rainforest exemplifies the large impacts of such growth on ecosystems and the environment (*8*). Cultivated soybean area in these parts of Brazil doubled over the past decade to 21 million ha and is expected to expand by another 40 million ha, or perhaps more if current Amazonia deforestation rates continue (*9*). These areas are supplying feed to the growing livestock industry in Brazil, China, India, and other parts of the world with unmeasured and often irreversible consequences on biodiversity, climate, soil, and water quality (see figure, page 1621).

Industrial livestock operations also require large amounts of water, especially for feed production, and water quality is reduced through the release of nutrients, pathogens, antibiotics, and other chemicals via return flows. Nitrogen and phosphorous run-off results from both crop fertilization and animal production with the delinking of production systems. Animal waste consists mainly of water, which makes long-distance transportation of untreated manure from livestock facilities to fields unprofitable. Nitrogen volatilized and leached from field crops and animal wastes has become a major source of aquatic dead zones, noxious odors, and ecological change (*10*). Industrial livestock expansion in China, Thailand, and Vietnam along the South China Sea is contributing to red tides and degrading water and sediment quality in one of the world's most biologically diverse shallow-water marine areas (*1*).

Expanding trade in meat products obscures the environmental and resource costs of livestock production, particularly for meat importers. Globally, trade in livestock products as a share of total production has almost doubled to 11% during the past 25 years (*3*). Steady growth in meat trade has resulted from advances in transportation, container systems, and cold storage technology; increasing specialization of production and processing operations; heightened consumer demands for product cuts, quality, and safety; low energy costs; and reduced trade barriers (*2*). Meat importers pay the direct costs of production and transportation, but do not pay the external resource costs, such as degraded water quality or biodiversity loss, which remain largely unaccounted for in the delinked livestock-crop systems.

A recoupling of crop and livestock systems is needed—if not physically, then through pricing and other policy mechanisms that reflect social costs of resource use and ecological abuse. Such policy measures should not significantly compromise the improving diets of developing countries, nor should they prohibit trade. They should focus instead on regulatory and incentive-based tools to encourage livestock and feed producers to internalize pollution costs, to minimize nutrient run-off, and to pay the true price for water. They also need to be accompanied by other methods to reduce the waste burden, such as the use of enzymes and synthetic amino acids to improve feed conversion (*11*). Without improved policies on waste treatment and on land and water pricing, net importers of meat and feedstuffs will continue to tax the resource base of exporting areas, either within the same country or abroad.

As an example of recoupling, the Netherlands has experimented with a set of policies that includes a tradable quota for hog production, manure disposal contracts, and a nutrient accounting system that tracks nitrogen inputs and outputs per farm (*12*). The cost to producers has been roughly $4/hog—33% more than in the most restrictive U.S. states (*2*). Owing to high administrative and production costs, these output controls will be replaced by limits on fertilizer and manure use in agriculture in 2006 (*12*). In the United States, the Environmental Quality Incentives Program in the 2002 Farm Bill provides funds for livestock producers to redesign manure pits and treat wastes (*13*). Cost-sharing programs exist at the federal and state levels to improve water management, to plant buffer strips, and to introduce combined chemical and irrigation systems. Waste discharge from livestock systems is regulated through the Clean Water Act at the federal level, and some states, such as Nebraska, enforce tougher restrictions than the federal standards (*14, 15*). Although these measures are a step in the right direction, other states, such as North and South Carolina, have more lenient environmental restrictions on livestock, and producers throughout the United States do not pay the true economic and ecological cost of water use and nitrogen runoff.

Although efforts to recouple are being pursued in some rich countries, the challenge is more daunting in developing countries where environmental legislation tends to be weak and funds for incentive-based programs are limited. Introducing codes of conduct, including careful siting of livestock operations, could reduce waste problems, and certification programs could be developed to encourage improved husbandry practices. In areas where new land is being cleared for feed crop production, such as Brazil, the costs of losing biodiversity and ecosystem services such as climate regulation should be considered explicitly in development plans. A strong political will is needed in all cases to implement conservation and environmental policies at the partial expense of producer income and foreign exchange earnings.

At a global scale, linking livestock to land would require the difficult task of harmonizing production, resource, and waste standards at higher levels than are seen in most countries currently. If the major meat- and feed grain–producing countries were to invoke strict environmental and resource standards, international meat prices would almost surely rise, perhaps slowing the increase in demand. Such a transition would be made easier politically if consumers increasingly demanded meat products based on sound environmental practices. In a global economy with no global society, it may well be up to consumers to set a sustainable course.

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MATERIALS SCIENCE

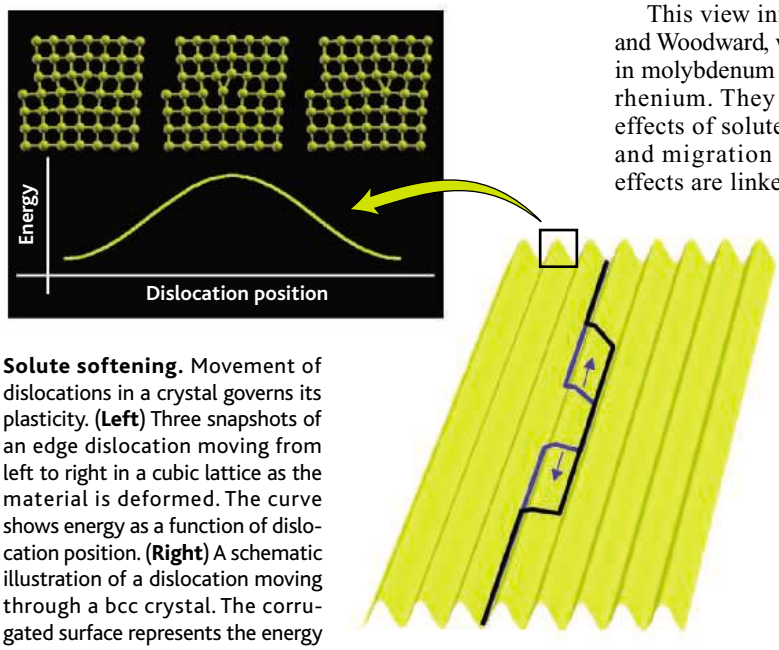
Metallurgy in the Age of Silicon

D. C. Chrzan

With the dawn of the Bronze Age some 5000 years ago, humankind learned that mixing two metals together can result in a material that is stronger than either of its constituents. Since then, metallurgists have been creating and exploring the properties of metallic alloys. Even in modern times, this practice can lead to curious results that appear to conflict with the collective wisdom of 5000 years of research. On page 1665 of this issue, Trinkle and Woodward (*1*) explain one of these outstanding puzzles—the solute-induced softening of some elemental metals.

One of the earliest recorded experiments with implications for the present discussion is that of Leonardo da Vinci. Da Vinci used a clever apparatus to measure the strength of metal wires as a function of their length. He found that longer wires were weaker, a result that puzzled experimenters through the early 20th century (*2*). A moment's thought, however, provides the explanation for da Vinci's result. A wire is imperfect—it contains defects of varying strength that weaken it. Like a chain, the wire is only as strong as its weakest link. Since a longer wire has more defects, it will have, on average, a weaker defect than a similar shorter wire, and will fail under a smaller load. Hence, da Vinci made it plan that mechanical strength is controlled by defects.

Models of strength must accurately predict the structures and dynamics of defects within a metal. A good starting point is the consideration of the stress required to shear a solid to its elastic limit. Early estimates indicated that a solid should yield at a stress equal to roughly one-fifth of its shear modulus (*3*). Experiment, however, reveals that metals often deform plastically at stresses closer to one-thousandth of their shear modulus. This observation led Orowan, Taylor, and Polyani to postulate [nearly simultaneously in 1934 (*4*)] that the motion of dislocations mediates plastic deformation (see the figure, left panel). This postulate is arguably a founding principle of modern metallurgy: To increase the plastic strength of a material, one need only impede the motion of dislocations. To decrease the plastic strength of a material, one must make the dislocations more mobile.



Solute softening. Movement of dislocations in a crystal governs its plasticity. (**Left**) Three snapshots of an edge dislocation moving from left to right in a cubic lattice as the material is deformed. The curve shows energy as a function of dislocation position. (**Right**) A schematic illustration of a dislocation moving through a bcc crystal. The corrugated surface represents the energy for the moving dislocations, which tend to lie in the minima. After a double kink pair (blue) is nucleated, the kinks migrate (black) so that the dislocation moves from one minimum to another.

Within a classical metallurgist's view, the influence of solute on the strength of a material is clear. Solutes break the translational symmetry of the crystal, and serve as obstacles to dislocation motion. Consequently, solutes strengthen alloys. Given this logic, it is surprising—and was a subject of some controversy—that various body-centered cubic (bcc) metals (*5*) and some semiconductors (*6*) display solute-induced softening. Though experimental evidence for this softening appeared as early as the 1940s, a detailed theoretical analysis would have to wait until the present day.

The proper framing of Trinkle and Woodward's theory requires a more detailed description of the dynamics of dislocations in bcc materials. Dislocations move on a corrugated potential surface dictated by the atomic-scale structure of the lattice. In bcc metals, the amplitude of the corrugation (called the Peierls energy) is substantial, forcing the dislocation to lie mostly at potential minima, with sections of the dislocation confined to different minima connected by kinks (see the figure, right panel). The dislocations move through the nucleation, and lateral motion of these kinks and the rates of these two processes govern the plastic strain rate of bcc metals.

This view informs the work of Trinkle and Woodward, who have studied softening in molybdenum alloyed with platinum and rhenium. They develop a theory for the effects of solutes on both kink formation and migration rates (*1*). Because these effects are linked so closely to chemistry, the best available theories rooted firmly in quantum mechanics are employed. Given the rapid advances in computational algorithms and hardware, one might expect to be able to compute directly the effects of solute atoms on dislocation dynamics. However, direct computation is not feasible because it requires far too many atoms, and integration times that far exceed those achievable. Thus Trinkle and Woodward develop an alternative approach. They begin with established continuum models for kink nucleation and migration rates, and then they compute solute-influenced parameters for these theories.

Trinkle and Woodward show that the kink nucleation rate is affected by solutes in two ways: Solutes can reduce the average (global) Peierls potential (see the figure, left panel), and solute/dislocation interactions affect (locally) the kink nucleation rate. The solute-induced change in the Peierls potential is obtained from the calculation of the Peierls misfit (*1*). These predictions, embodied in figure 2 of the Trinkle and Woodward report (*1*), are noteworthy for the following: (i) They are rooted firmly in quantum mechanics and the solution to Schrödinger's equation. There are no adjustable parameters in the theory. (ii) These are, even by modern

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standards, very expensive calculations. Computing the properties of a collection of 540 transition metal atoms is made possible only through the development of extremely efficient algorithms and very fast computers. These large calculations are necessary because the geometry of the dislocation couples with the chemistry to produce the final results. Similar calculations in the absence of the dislocation fail to produce the experimentally observed trends [see table S1 in the supporting online material (*1*)]. The quantum mechanical predictions are then incorporated into the kink nucleation rate, and yield the potential for solute-induced softening.

With the fundamentals of softening understood, Trinkle and Woodward need to account for the solute-induced strengthening effects observed at higher solute concentrations. In doing so, they rely on functional forms rooted in elasticity theory, an analysis of the statistics of pinning, and the direct computation of solute/dislocation interaction energies (again rooted firmly in quantum mechanics). The net result is a quantitative prediction of the softening/strengthening properties of solutes in molybdenum.

Trinkle and Woodward's research is appealing beyond the simple fact that they have solved one of the outstanding puzzles of metallurgy. Their study represents a remarkable application of three types of theories (quantum mechanics, statistical methods, and continuum dislocation theory) and a remarkable tool (a fast computer) to solve this metallurgical problem. The field of computational materials science has promised to aid in the design of structural materials for specific purposes. Though there is much more work to be done, Trinkle and Woodward have taken a small step toward this elusive goal. Their detailed theory of the interaction of solutes and dislocations provides a framework that a metallurgist can employ to improve materials properties. In doing so, they have provided an inkling into the practice of metallurgy in the age of silicon.

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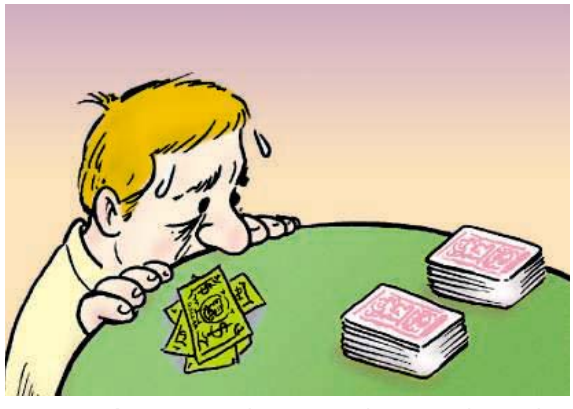
NEUROSCIENCE

Emotion and Reason in Making Decisions

Aldo Rustichini

Two decks of 100 cards each are on a table. The one on the right has 50 red and 50 blue cards; the one on the left also has red and blue cards, but I don't tell you how many of each. You pick one card from each of the two decks, without looking at the color. Now you can bet on the color of a card of your choosing between the two, and I will give you $100 if you guess right. Do you bet on the right or the left card? You may be inclined to choose the right. Before you answer, note that sheer logic dictates that you should consider the left one as just as good a bet too. Here is why. Choose the left deck, and flip a coin to choose a color. If the card is red, you will match the color with 50% probability. If it is blue, the same conclusion holds. Therefore, no matter what the color of the left card, you have a 50-50 chance of winning $100, which is also what the card on the right side will give you. Are you convinced? If not, are you willing to give me an extra dollar to get your preferred choice?



Decisions, decisions. Our brain treats choices involving risk or ambiguity differently.

Although the logic is impeccable, most people are not convinced and prefer to bet on the right deck because "they know the probability." They are also willing to pay to avoid the vagueness plaguing the left deck. If asked to pay, people offer around $42 for the left deck and $45 for the right deck. The right deck's average worth is $50; the $5 difference between the offer for the right deck and its average worth is what economists call the risk premium, a way to measure aversion to risk. The additional $3 difference between the prices offered for the two decks is the ambiguity premium, a measure of aversion to the vagueness of the probability. In real life, the ambiguity premium may be substantial. For instance, it is a large part of the difference between the higher price of stocks of domestic companies, as opposed to cheaper foreign ones: People like better what they know.

Economists in recent decades have realized [since (*1*)] that people are averse to ambiguity. To account for this behavior, they (*2*) have built and used a formal decision theoretic model. It formulates the idea that when the probability is not precise, people are inclined to consider the worst possible outcome of each action they can take as the outcome that will occur. In our example, if you choose the ambiguous card deck, the worst possible outcome for each color you choose is $0. You are facing a malevolent opponent who can choose the outcome that is least favorable to you.

This is now an accepted and widely applied model (*3*–*6*). But is this just a clever mathematical model, or does it correspond to a real process in the brain? This formal theoretic model of ambiguity aversion has two main predictions. The first is that subjects approach a decision with ambiguous probabilities in the same way as they do when they face a malevolent opponent. The second is that they deal with this situation as a calculated risk: In choosing with ambiguous probabilities, subjects estimate the worst case, how likely it is, and how much it pays. Dealing with decisions facing ambiguity is a process involving both emotion and reason. Is this what we observe?

On page 1680 of this issue, Hsu and colleagues (*7*) report on a functional magnetic resonance imaging study that may give us physiological clues as to the nature of ambiguity. The main result is that the brain treats the two card decks in the example above in different ways. Distinct areas of the brain are active when we evaluate ambiguous and risky choices. Moreover,

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patients with large lesions that incorporate one of these areas (the orbitofrontal cortex) treat ambiguous and risky choices differently from normal subjects.

Twenty-four different areas in the brain are more active under conditions of ambiguity than risk. Among these regions, Hsu *et al*. focused on those that previous researchers have, with some controversy, associated with the emotional side of decision-making. However, a large number of these areas (located in the temporal, parietal, and prefrontal lobes of the brain) deal with the estimation of the values of the options, which suggests that the decision process integrates emotional and computational components. The results confirm earlier findings that not only are ambiguity and risk treated differently by the brain (*8*), but so are related situations such as when one considers sure and risky outcomes, or monetary gains and losses (*9*). Taken together, these findings support the theory of ambiguity aversion that economists have described.

What is next? Elucidating the neural processes underlying decision-making may help us understand important economic differences between ambiguity and risk. Human attitude to risk fuels the substantial profits of two large business sectors of our economy—gambling and insurance. In contrast, there is no sector served specifically by our aversion to ambiguity. This difference between risk and ambiguity is related to an experimental fact: If I ask you to choose repeatedly among risky options, your risk premium remains stable. But recent experimental evidence (*10*) suggests that the ambiguity premium declines as subjects repeat their choices: People slowly adjust to ambiguity; they do not adjust to risk. Just as we learn to act optimally given the actions of others (the Nash equilibrium of game theory), by choosing repeatedly, one may be learning, slowly, to deal with ambiguity in our choices.

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ATMOSPHERIC SCIENCE

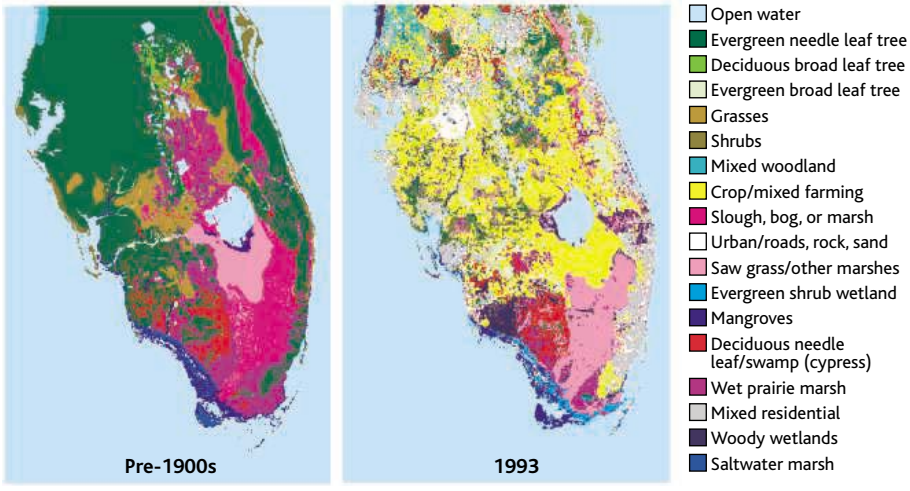
Land Use and Climate Change

Roger A. Pielke Sr.

Change and variability in land use by humans and the resulting alterations in surface features are major but poorly recognized drivers of long-term global climate patterns (*1*, *2*). Along with the diverse influences of aerosols on climate (*1*, *3*, *4*), these spatially heterogeneous land use effects may be at least as important in altering the weather as changes in climate patterns associated with greenhouse gases. On page 1674 of this issue, Feddema *et al*. report modeling results indicating that future land use and land cover will continue to be an important influence on climate for the next century (*5*). One implication of this work is that the Intergovernmental Panel on Climate Change (IPCC), which has yet to appreciate the significance of the full range of phenomena that drive climate change, risks rapidly falling behind the evolving science if this effect is not included. Although the impact of land use and land cover on the atmospheric concentration of carbon dioxide and methane, and on the global average surface albedo, have been included in international climate change assessments (*6*), the role of land use and land cover change and variability in altering regional temperatures, precipitation, vegetation, and other climate variables has been mostly ignored.

The importance of land use and land cover change and variability should not be a surprise. On the basis of research by Avissar and co-workers at Duke University, NASA reports that "scientists estimate that between one-third and one-half of our planet's land surfaces have been transformed by human development" (*7*). A large body of research has documented the major role of land use and land cover change and variability in the climate system (*8*–*12*).

One example of how land use and land cover affects global climate is the changing spatial and temporal pattern of thunderstorms. Land use and land cover change and variability modify the surface fluxes of heat and water vapor. This alteration in the fluxes affects the atmospheric boundary layer, and hence the energy available for thunderstorms. As shown in the pioneering work of Riehl and Malkus (*13*) and Riehl and Simpson (*14*), at any time there are 1500 to 5000 thunderstorms globally (referred to as "hot towers") that transport heat, moisture, and wind energy to higher latitudes. Because thunderstorms occur over a relatively small percentage of Earth's surface, a change in their spatial patterns would be expected to have global climate consequences. The changes in the spatial patterning of thunderstorms result in regional alterations in tropospheric heating that directly change atmospheric and ocean circulation patterns, including the movement and intensity of large-scale high- and



Changing surface patterns. Vegetation classification of the Florida peninsula before 1900 (**left**) and in the 1990s (**right**), which shows the dramatic conversion of the region's landscape during the 20th century. [Reprinted from (*21*) with permission]

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low-pressure weather systems (*15*). Most thunderstorms (by a ratio of about 10 to 1) occur over land (*16*), and so land use and land cover have a greater impact on the climate system than is represented by the fraction of area that the land covers.

To understand how these changes are important, consider the analogy of the global effects of the El Niño–Southern Oscillation (ENSO), a regional phenomenon of the Pacific Ocean. ENSO events have global effects because they are of large magnitude, have long persistence, and are spatially coherent (*17*). Land use and land cover change and variability have spatial scales similar to those associated with the sea surface temperature anomalies of an ENSO (*18*, *19*). This climate phenomenon also is of large magnitude, has long persistence, and is spatially coherent. Thus, land use and land cover have a first-order role as a climate-forcing effect, as Feddema *et al*. further demonstrate (*1*). Feddema *et al*. used the U.S. Department of Energy Parallel Climate Model (DOE-PCM) to perform climate change simulations with different scenarios of landscape change during the current century. Their study shows that future land use decisions can alter IPCC climate change simulations from those based solely on atmospheric composition change.

To keep up with evolving science, the IPCC assessment currently under way should include land use and land cover change and variability as a first-order climate forcing, along with the other spatially heterogeneous climate forcings as identified in a recent report of the National Research Council on radiative forcing (*1*). To fully consider the effects of land use and land cover on climate, the IPCC also should move beyond globally and zonally averaged temperatures as the primary climate metric. Although the globally averaged surface temperature change over time may in fact be close to zero in response to land use and land cover change and variability, the regional changes in surface temperature, precipitation, and other climate metrics can be as large as or larger than those that result from the anthropogenic increase of well-mixed greenhouse gases. Moreover, people and ecosystems experience the effects of environmental change regionally, and not as global averaged values.

The issue of a "discernable human influence on global climate" (*20*) misses the obvious, in that we have been altering climate by land use and land cover change since humans began large-scale alterations of the land surface. The Feddema *et al*. study shows that we will continue to alter the regional and global climate system in the 21st century, and these changes will act as a climate-forcing effect. Such changes are bound to complicate any efforts to stabilize the climate system that focus only on a subset of first-order climate forcings.

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NEUROSCIENCE

Synaptic Membranes Bend to the Will of a Neurotoxin

Joshua Zimmerberg and Leonid V. Chernomordik

Discovery in neurobiology is replete with examples of scientists using toxins that bind, neutralize, or cleave physiologically important cellular proteins. The inhibitory binding of saxitoxin and tetrodotoxin to the sodium channel, conotoxin and spider toxins to the calcium channel, α-bungarotoxin to the acetylcholine receptor, and clostridial toxins to SNARE proteins that facilitate high-fidelity membrane fusion—these toxins were not only instrumental in their respective isolation and investigation but enabled the dissection of basic cellular and physiological mechanisms. On page 1678 in this issue, Rigoni *et al.* (*1*) report how the action of phospholipase A2, a neurotoxic component of snake venom that paralyzes the neuromuscular junction, reveals a new regulatory mechanism for neurotransmitter release at the synapse. Lysophospholipids and free fatty acids, the hydrolytic products of this lipase, alter the energetics of the presynaptic membrane, thus affecting its disposition to bend and fuse with synaptic vesicles. This finding may not only explain the long-standing mystery of the molecular mechanism of action of presynaptic neurotoxins that have phospholipase A2 activity, but it also demonstrates the critical importance of membrane lipid composition for synaptic activity.

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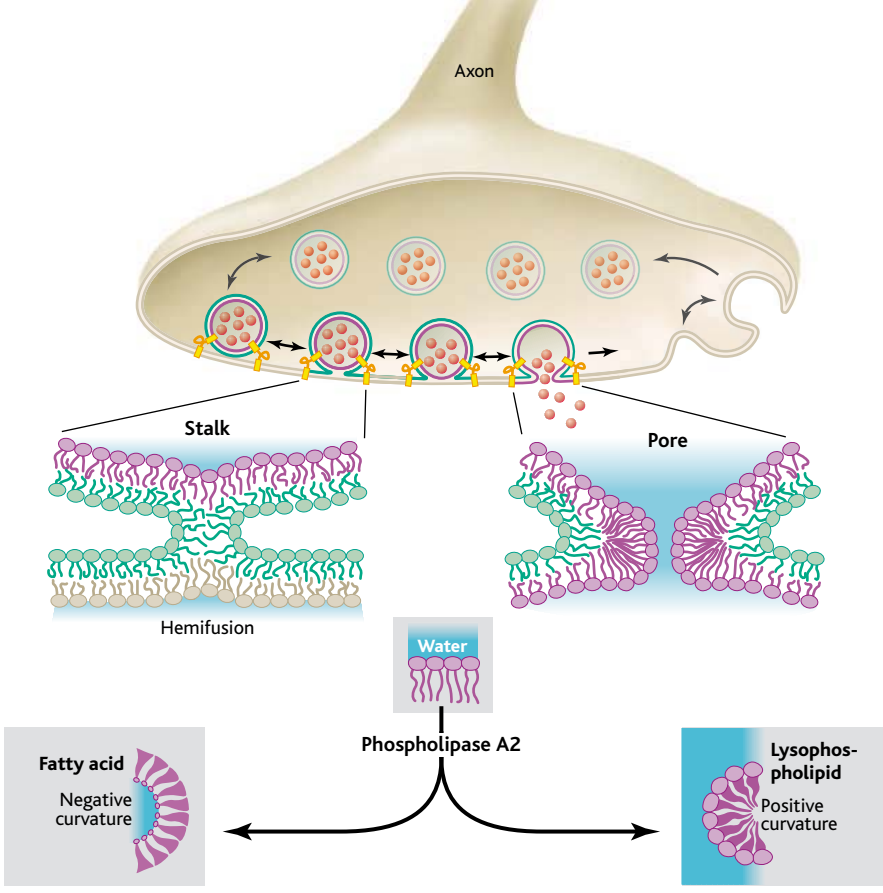
Phospholipase A2 hydrolyzes stable membrane lipids into lipids that cannot form bilayers. Rather, the lipid products form micelles (lysophospholipids) and inverted micelle-like structures (fatty acids) that reveal a positive and negative spontaneous monolayer curvature, respectively (*2*, *3*) (see the figure). Our current understanding of the molecular pathway of biological membrane fusion began with experiments in which these curvature-promoting lipids revealed curvature-sensitive intermediates during calcium-dependent exocytosis, intracellular vesicle trafficking, and virus–host cell membrane fusion (*4*, *5*). In a "hemifusion intermediate" (*6*–*9*), the contacting leaflets of two apposing membrane bilayers merge. Negative-curvature lipids such as unsaturated fatty acids promote hemifusion, but positive-curvature lysophospholipids inhibit this process (*6*). In contrast, the opening of a fusion pore within the hemifusion structure (the pore connects the two aqueous environments delineated by the two apposing membranes) depends on the lipid composition of the distal monolayers of the membrane bilayers. Opening of a fusion pore is inhibited by unsaturated fatty acids but promoted



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Lipids alter membrane bending at the synapse to control vesicle fusion and synaptic activity. Membrane fusion between a synaptic vesicle containing neurotransmitter molecules (red) and the plasma membrane of a presynaptic neuron is hypothesized to proceed through the formation of a hemifusion intermediate followed by the formation and expansion of a fusion pore. Lipid mixing between the inner (purple) and outer (green) leaflets of the vesicle membrane and plasma membrane (tan) at early fusion stages is likely restricted by the proteins (yellow ribbons) surrounding the fusion site. The connection between contacting leaflets of two bilayers (the stalk) is favored by lipids that support negative leaflet curvature. In contrast, the curvature of the edge of the fusion pore, formed by distal bilayer leaflets brought together by hemifusion, is favored by positive curvature lipids. Phospholipase A2 cleaves lipids that form flat monolayers into fatty acids (negative curvature) and lysophospholipids (positive curvature).

by lysophospholipids. Thus, biological membrane fusion is essentially lipidic in nature, but catalyzed by proteins.

Most importantly for neuronal function, if a fraction of the synaptic vesicles are even transiently hemifused with the presynaptic membrane, they are at the penultimate stage of exocytic fusion, awaiting fusion pore formation and poised to release transmitter very quickly (*10*). Thus, hemifusion can explain the extremely fast kinetics of neurotransmitter release (<100 μs after the intracellular calcium concentration rises) that characterize synaptic exocytosis. The prediction that synaptic vesicles at the active zone make transient hemifusion intermediates (see the figure) also can explain the spontaneous release of neurotransmitter from vesicles (miniature postsynaptic currents, or minis) that is a hallmark of synaptic activity. Hemifusion intermediates between a vesicle and a planar membrane also display spontaneously occurring fusion pores that link the aqueous interior of the vesicle with the aqueous space across the planar membrane (*11*).

At the synapse, it is not yet clear how lysophospholipids or fatty acids increase neurotransmitter release. Do they act on a transient hemifusion intermediate between a synaptic vesicle and the presynaptic membrane at the active zone to directly increase the likelihood of fusion pore formation? Or do they act indirectly by increasing the resting permeability of lipidic pores in the presynaptic membrane to calcium, thus enhancing calcium-triggered exocytosis? Further work is required to determine the role of calcium in the action of different phospholipase A2 toxins and the products of lipid hydrolysis. Nevertheless, after release, lysophospholipids and fatty acids apparently inhibit the next stage in synaptic vesicle dynamics—endocytosis. The continual presence of previously intravesicular proteins at the outer surface of the presynaptic membrane suggests that changes in membrane curvature block vesicle internalization and recyling. This may be due to phospholipase A2 activity and its hydrolytic products, which bend membrane bilayers outward (*12*), opposing invagination of the plasma membrane into a budding endocytic vesicle.

Do eukaryotic cells change their own membrane lipid composition to regulate intracellular fusion? Phospholipases A2, C, and D, and their lipid products such as arachidonic acid, have been implicated in membrane traffic control (*12–16*). For instance, phospholipase A2 and lysophospholipids promote sperm acrosomal exocytosis (*16*), and phospholipase C and diacylglycerol are implicated in nuclear envelope assembly (*13*). Because lipids that promote bending of membrane leaflets into fusion intermediates destabilize the membrane bilayer, any physiological changes in lipid composition must be correctly localized in space and time. Localizing the phospholipase to a specific site would not ensure a sufficient change in lipid monolayer composition, because the lateral mobility of lipids is high and concentrating phospholipase hydrolysis products costs entropy. In general, the turnover rate of phospholipases is slow compared to the rate of lateral lipid diffusion. Membrane proteins, and the lipid clusters they reside in, might serve as a barrier to lipid redistribution and facilitate local lipid accumulation. Restriction of lipid flux through early fusion intermediates is experimentally observed (*4, 17, 18*), and domain structures are important for viral fusion (*19*).

Thus, the energetics imparted by lipids to bilayers are critical to membrane dynamics. Future work may uncover how and when changes in lipid composition in each leaflet are organized by cells to optimize cellular processes.

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Restoration of Degraded Tropical Forest Landscapes

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The current scale of deforestation in tropical regions and the large areas of degraded lands now present underscore the urgent need for interventions to restore biodiversity, ecological functioning, and the supply of goods and ecological services previously used by poor rural communities. Traditional timber plantations have supplied some goods but have made only minor contributions to fulfilling most of these other objectives. New approaches to reforestation are now emerging, with potential for both overcoming forest degradation and addressing rural poverty.

One of the defining events of the past century was the astonishingly rapid decline in the extent of tropical forests. An estimated 350 million hectares have been deforested, and another 500 million hectares of secondary and primary tropical forests have been degraded (*1*). The damaging consequences of this include the loss of ecological services (such as biodiversity and watershed protection), the loss of many goods (such as timber and nontimber forest products), and the loss of means of existence for forest-dwelling people. These losses have fallen particularly heavily on the rural poor in tropical countries, where the livelihoods of at least 300 million people now depend upon these degraded or secondary forests (*1*).

Until recently there were three major responses to this process of forest degradation. One was to expand networks of protected areas to help protect the remaining biodiversity. In this response, the focus has largely been on making the selection of candidate sites as representative and comprehensive as possible (*2*). A second was to improve agricultural productivity on abandoned lands in order to improve the livelihoods of communities living in these areas. The third approach has been to undertake some form of reforestation. Much of this has been done with the use of industrial monocultures involving a limited number of species from a remarkably small number of genera (particularly *Pinus*, *Eucalyptus*, and *Acacia*). Although many of these plantations have been productive and generated goods such as pulpwood, few provide the variety of goods (e.g., timbers, medicines, and foods) once provided by the original forests to the people living in these areas.

Neither agricultural development nor past forms of reforestation have been sufficient to provide sustainable livelihoods and environmental services over the large areas of degraded land that have developed. Despite the expansion of protected area networks, there has been an overall gradual simplification and homogenization of some of the world's most biologically diverse landscapes. It is unclear just what the long-term consequences of this might be.

In recent years, new forms of reforestation have been tested that may offer additional ways of dealing with degraded tropical forest landscapes. These include improvements in the management of secondary or regrowth forests as well as more complex forms of reforestation where forest cover has been entirely lost [Supporting Online Material (SOM) Text]. There is clear evidence that biodiversity conservation can be enhanced by the careful location of protected areas (*2*). Likewise, improved methods of regrowth management and reforestation should also help restore biodiversity to degraded landscapes (Fig. 1).

Accelerating Natural Recovery

One way of increasing forest cover is to protect and manage the large areas of secondary or regrowth forests now present. Not all degraded lands are completely deforested, and they vary in forest cover, degree of fragmentation, and extent to which biodiversity has been lost. They also vary in their capacity to recover unaided if further disturbances can be prevented. Successional development (or self-repair) can be rapid at sites where forest clearance has occurred relatively recently (years versus decades); where some residual trees, seedling banks, and soil seed stores composed of native species remain; and where intact, biodiversity-rich native forests are still present in the landscape. Well-documented examples where natural regeneration has occurred over very large areas are Puerto Rico (*3*), Tanzania (*4*), Costa Rica (*5*), and Brazil (*6*). Species-rich forests can develop in this way, but such forests often contain only a subset of the original plant or wildlife species (*3*, *7*). Although it is rarely possible to determine the proportions or identities of missing plant species, the most common absentees are the large-fruited plant species because of the absence of appropriate dispersal agents. Foresters have sought to increase the populations of commercially important timber species in such secondary forest by enrichment planting (planting target species under canopy gaps or along cleared strips) (Fig. 2). The same technique might be used to improve biodiversity by adding species that are otherwise unable to colonize and regenerate or are ecologically threatened or vulnerable.

Natural recovery of degraded forest areas is not inevitable, and recovery is difficult where the system has crossed an ecological threshold and reached a new steady state con-

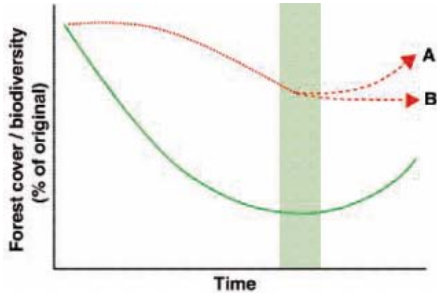

Fig. 1. A conceptual diagram of changes in forest cover in a landscape over time as a consequence of agricultural intensification. Forest cover is shown as a solid line, and the corresponding change in biodiversity is shown as a dotted line. Biodiversity loss occurs as forest cover declines, although the magnitude of this loss depends on the extent and location of the protected area network. When reforestation begins to occur (shaded area), it will increase forest cover, but any corresponding improvement in biodiversity depends on the types of reforestation carried out. Trend A depicts a scenario where secondary forest is protected and where connectivity is enhanced by reforestation using a diverse range of native species; trend B, where reforestation relies solely on extensive monoculture plantations of fast-growing exotic species.

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dition (*8*, *9*). A common example is when degradation leads to topsoil loss and a reduction in soil fertility, complicating recolonization of these sites for many of the original species. Another threshold is commonly crossed when sites become occupied by grasses. This increases the risk of wildfires, particularly in the seasonal tropics, which then reduces woody plant recruitment and favors the further spread of grasslands. There are many examples throughout the tropics of extensive grasslands that persist over time despite being entirely surrounded by forests (*10*). Therefore, even though natural regeneration is potentially the cheapest way of fostering reforestation over large areas, it is also the riskiest option because thresholds may have been crossed or because excluding further disturbances is difficult (*9*).

Plantings and Plantations

Most deliberate efforts to overcome degradation involve tree planting. However, even traditional forms of timber plantation can be risky operations, and, where species selection or early stand management are inappropriate, plantations can fail (*11*, *12*). Planting to generate ecological services as well as goods is even more difficult, because trade-offs must be made between the productivity of desired goods (i.e., timber) and provision of ecological services (i.e., biodiversity) and the techniques to achieve these simultaneous goals are still being developed. Some of the approaches are summarized in Table 1, which also shows their capacity to supply services as well as goods. The choice of approach will depend on the socioeconomic circumstances of the land owner as well as on the ecological situation (soil fertility, extent to which natural forest remnants remain in the landscape, etc.) (*13*).

Restoration plantings. The most ambitious goal is to attempt to reestablish the original forest ecosystem. Although the rules of ecosystem assembly are still debated (*14*), there are some empirical data from several sites showing promising results (*15*–*17*). Two broad approaches have been tested. Each involves a contrasting assembly rule, but each appears to offer promising results under appropriate conditions.

One approach is to use a small number of fast-growing but short-lived tree species (i.e., equivalent to early successional pioneer species) to create a canopy cover. These shade out grasses and weeds, diminish the fire hazard, and facilitate colonization of the site by a wider range of species from nearby intact forest (*1*, *16*). Under certain circumstances, these cover or nurse trees might be established by direct seeding (*18*). The success of this low-diversity planting technique depends on the ability of additional native species to reach the site from nearby intact forest, principally through seed dispersal by frugivorous birds and mammals. In such cases, small-fruited species are generally more likely to colonize than large-fruited species. The approach also runs the risk of facilitating colonization by undesired weed species.

The other approach uses a much greater number of species representative of more mature successional stages and bypasses the natural successional sequence. Plantings are usually at high densities (>2500 trees per ha), and competitive interactions determine the final forest composition (*19*). Species unable to tolerate open planting can be added once canopy closure has occurred, either as seedlings or by direct seeding. Such an approach was used in a forest restoration program after bauxite mining in central Amazonia (SOM Text). In this case, over 160 species representing a range of life forms and successional stages were planted after mining ceased and topsoil replaced (Fig. 3). After 13 years, the new forest, enriched by colonization by species from nearby intact forests, resembled the undisturbed forest in its tree species composition, although structural recovery is still incomplete (*18*). The approach allows key species to be targeted (e.g., large-fruited species) but requires sufficient ecological knowledge to be able to collect seeds and germinate large numbers of seedlings from a wide variety of species.

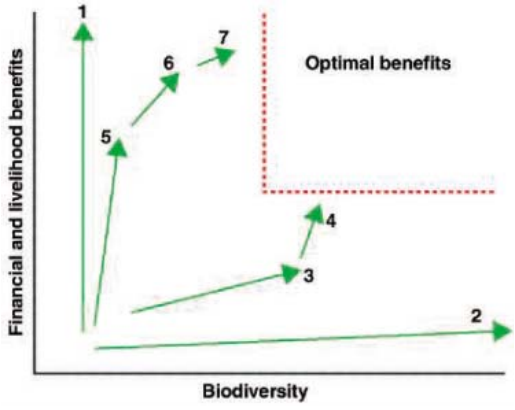

Fig. 2. It is difficult to develop restoration methods at a particular site that optimize financial and livelihood benefits as well as generate improvements in biodiversity (top right corner). Traditional monoculture plantations of exotic species (arrow 1) mostly generate just financial benefits, whereas restoration using methods that maximize diversity and (arrow 2) enhance biodiversity yields few direct financial benefits to landowners, at least in the short term. Protecting forest regrowth (arrow 3) generates improvements in both biodiversity and livelihoods, although the magnitude of the benefits depends on the population density of commercially or socially important species; these can be increased by enrichment of secondary forest with commercially attractive species (arrow 4). Restoration in landscapes where poverty is common necessitates attempting both objectives simultaneously. But, in many situations, it may be necessary to give initial priority to forms of reforestation that improve financial benefits, such as woodlots (arrow 5). In subsequent rotations, this balance might change over time (moving to arrow 6 and later to arrow 7 by using a greater variety of species). There may be greater scope for achieving multiple objectives by using several of these options at different locations within the landscape mosaic.

The key limitation to the use of such restoration plantings is their high cost (*20*). They do not supply significant volumes of commercially useful goods such as timber, and usually there are only limited markets for the ecological services they provide. Hence, restoration plantings are probably an option that can only be used in a relatively small number of situations and rarely in the most severely degraded tropical landscapes, except where the potential environmental benefits or costs of inaction (as in mined land or mangrove restoration) may justify the required investment (SOM Text).

Plantation establishment to provide goods and ecological services. An alternative is to establish plantations that provide goods for which there is a market, such as timbers, but also generate a larger range of ecological services than the more traditional industrial timber plantations. This approach seeks a balance between the financial benefits of industrial timber plantations (which enable large areas to be reforested) and the biodiversity gains possible from carrying out a more complete ecological restoration.

The simplest way this might be done is to use monocultures of native species (particularly those that are fleshy-fruited or have propagules dispersed by forest wildlife) rather than exotics. Although the biodiversity gains are modest, they are more likely to create environmental conditions that are suitable for native fauna than plantations of exotic species. Such trials involving monoculture plantations of high-value native timber species are now under way in many countries (SOM Text). Another approach is to use mixtures of species rather than simply monocultures (*21*). Recent experiments in Costa Rica (*22*, *23*) on commercially attractive native tree species suggest that mixtures in the dry and humid tropics have the potential to offer a number of benefits over monocultures, including production gains and reduced insect damage. Another advantage of mixtures is that they might provide small landowners a form of insurance to protect them from uncertain future markets. However, the design of these mixtures poses several key dilemmas. One question is how many species are needed to maximize these benefits; that is, what is the nature of the relationship between increased diversity and any functional benefits?

Table 1. A summary of some of the different forms of reforestation that might be used when secondary forests are present or when some form of planting is needed. Any combination of these techniques could be used in degraded landscapes depending on ecological circumstances and on the goals of the land managers.

Natural secondary forests	Plantings and plantations	
	To restore biodiversity	To supply goods and ecological services
Protect and manage natural regrowth: Potentially able to supply a variety of goods and services depending on the age and condition of the forest.	Restoration plantings using small number of short-lived nurse trees: Acquisition of further diversity dependent on colonization from nearby forest remnants. Primary benefit is ecological services although can supply some goods depending on species present.	Tree plantation monoculture of exotic species: An efficient method of timber or food production for (mainly) industrial users; in most circumstances it is less successful in supplying many services.
Protect and manage natural regrowth plus enrichment with key species: Enrichment with commercially, socially, or ecologically useful species can improve the value of these forests to local communities or industry.	Restoration plantings using large number of species from later successional stages: Higher initial diversity that will also be supplemented by colonization from nearby forest remnants. Primary benefit is ecological services although can supply some goods depending on species used.	Tree plantation monoculture of native species: Useful to supply timbers of higher commercial value and other goods such as fruits, nuts etc.; the longer rotations normally used may facilitate an improved supply of ecological services such as watershed protection.
	Direct seeding: The number of species that can be established by direct seeding is limited by seed supply but the establishment cost can be lower. Direct seeding can be used to initiate reforestation in open fields under appropriate conditions but it may be most useful when used to enhance diversity once some tree cover is already present.	Tree plantation used as a nurse crop with underplantings of native species not otherwise able to establish at the site: An initial fast-growing nurse crop supplying commercially useful timbers or other goods can facilitate (e.g., via nitrogen fixation and microclimate alterations) the subsequent establishment of more species-rich forests that supply a wider range of goods and services.
		Tree plantation mixtures of native species: Mixed-species plantations can, potentially, supply a wider range of goods and services than monocultures. Biodiversity gains are greater than in plantation monocultures but are mostly still modest (usually less than five planted species).

Although there is increasing evidence that functions such as production, litter decay, and nutrient cycling can be enhanced as diversity increases (*24*), there is also increasing acceptance that simple taxonomic differences are an incomplete measure of diversity. Responses may depend more on the diversity of functional groups (e.g., nitrogen fixers, slow- or fast-growing canopy trees, and bird-attracting species) or on the diversity of functional responses within these groups rather than simply on the number of tree species used in a plantation (*8*). But our incomplete knowledge of tropical forest flora means it is rarely possible to confidently categorize many species into various functional groups apart from relatively simple categories. Nor, for the same reason, is it yet possible to define species within a particular functional group that might have different functional responses.

A second dilemma facing those wishing to use mixed species plantations is that of identifying species able to form stable mixes (i.e., able to avoid one species outcompeting and excluding others). It is clear that the nature of the diversity-function relation depends on the particular species used and that the sampling effect can alter this relation (*25*). These theoretical problems are matched by some practical ones as well. Unless the market prices of the various species are similar, the overall value of the plantation will be reduced as increasing numbers of lower value species are added.

This means there may be a limit on the use of plantations to foster biodiversity at a particular site, although such plantations often catalyze successional development in the plantation understory (*26*). Trying to strike compromises between conservation and economically valued production may end up generating suboptimal outcomes for each. Nevertheless, mixtures may be useful if they are likely to enhance both ecological resilience and financial resilience of these new systems. The latter would come from the greater diversity of income streams available to the landowner.

Making Reforestation Attractive to Rural Communities

The present scale of land degradation is such that it will only be overcome if large numbers of individual landowners or land managers become involved in reforestation. But, large-scale tree planting or farm forestry is not commonly practiced by rural communities living in degraded landscapes, even though many might practice some form of agroforestry. This may be because most of their land is needed for food production, but it is also because many rural people still have insecure land and tree tenure and are unwilling to invest in an activity from which they may derive little benefit. Reforestation can also be unattractive because the initial costs can be high, whereas the direct financial benefits are delayed in comparison with a variety of other possible land uses the landowner might

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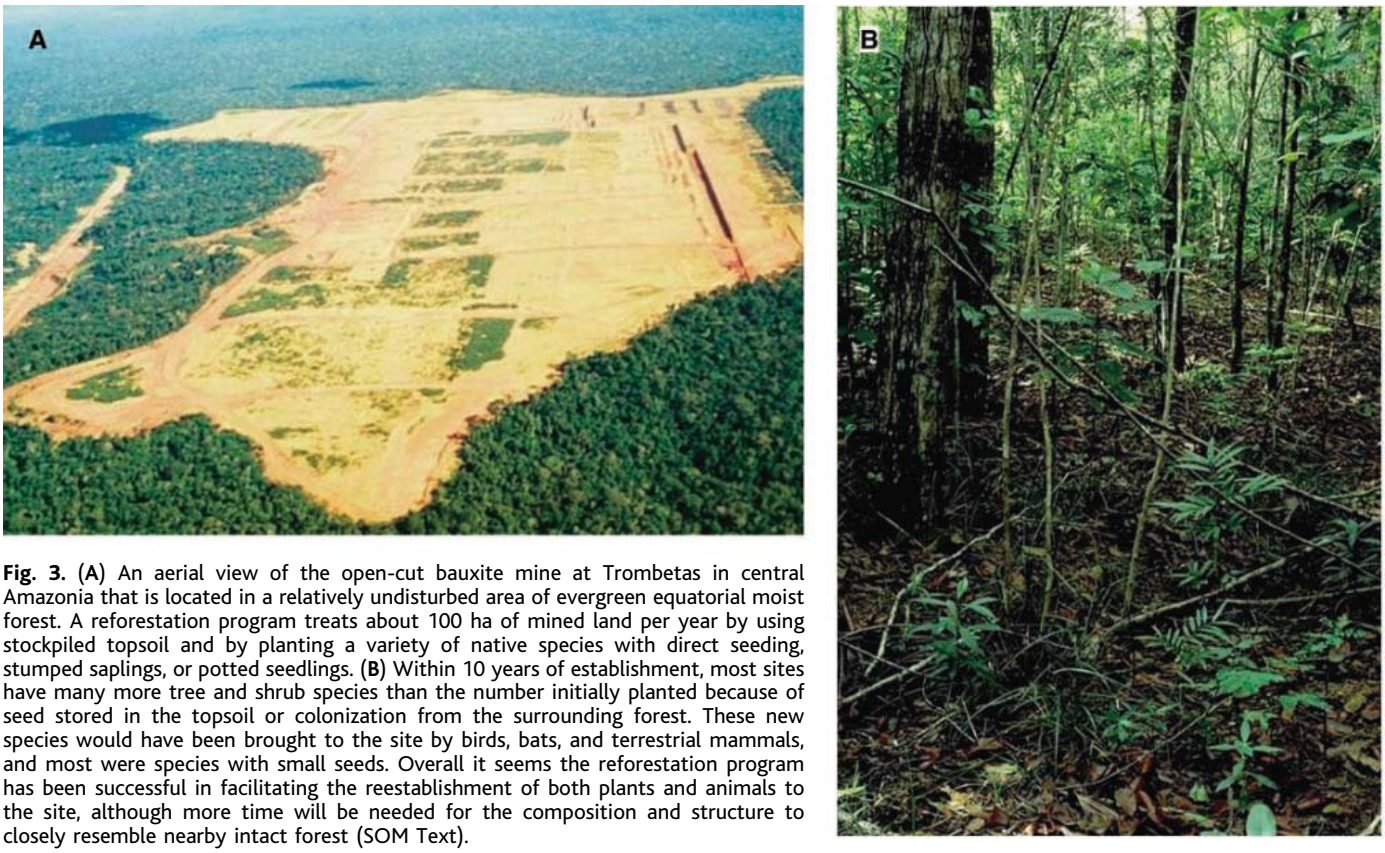

Fig. 3. (**A**) An aerial view of the open-cut bauxite mine at Trombetas in central Amazonia that is located in a relatively undisturbed area of evergreen equatorial moist forest. A reforestation program treats about 100 ha of mined land per year by using stockpiled topsoil and by planting a variety of native species with direct seeding, stumped saplings, or potted seedlings. (**B**) Within 10 years of establishment, most sites have many more tree and shrub species than the number initially planted because of seed stored in the topsoil or colonization from the surrounding forest. These new species would have been brought to the site by birds, bats, and terrestrial mammals, and most were species with small seeds. Overall it seems the reforestation program has been successful in facilitating the reestablishment of both plants and animals to the site, although more time will be needed for the composition and structure to closely resemble nearby intact forest (SOM Text).

adopt (i.e., reforestation can have high opportunity costs). Even when tree planting is undertaken, most landowners have often found it easier to use fast-growing exotic tree species than native species, about which there is much less ecological or silvicultural knowledge.

There are several ways by which reforestation might be made more attractive to landowners. One is to develop appropriate institutional, legal, and policy settings (e.g., providing secure land tenure, elimination of "perverse" incentives that favor deforestation and forest degradation, and facilitating marketing of forest goods) and to provide financial loans or inducements to make reforestation attractive.

Another is to provide more information and technical assistance to landowners or communities about the species suitable for planting, their silvicultural requirements, and their market values. In many cases, the market prices of timber from slower growing native species are significantly higher than those for fast-growing exotics, and these prices are increasing as supplies from natural forests decline (*27*). As the supplies of low-value timbers from large industrial plantations flood the international markets, the market niche for these high-quality timbers may be a safer and more valuable target for smallholders. Experience to date suggests that smallholders who plant native tree species often prefer to use more than one species because they are interested in producing a variety of goods (*13*).

A third way to make reforestation attractive is to develop silvicultural systems by which plantations can be underplanted with crops that mature more quickly than trees, building on traditional and modern knowledge of agroforestry systems. These might be shade-tolerant agricultural cash crops (e.g., coffee, cocoa, and cardamom) or nontimber forest products such as rattans or medicinal plants (*28*). Again, there is often a significant local market for these species as supplies previously obtained from natural forests decline.

Lastly, reforestation might be more attractive to landowners if they are paid for the ecological services provided to those who benefit from reforestation but who share neither the costs nor risks. Examples of payments for ecological services provided by plantations include water, carbon, and biodiversity (*29*). Such payments could make reforestation quite an attractive land use. Although this market has undergone significant growth in the past decade, fundamental relations between forest composition/structure and their functional characteristics, i.e., their "yields" of ecological services, are still poorly understood. This contributes to the uncertainty of the market value of these services. Further, the legal frameworks to allow trading are yet to be established in most tropical countries, and many of these markets are likely to have high transaction costs. This is particularly the case in landscapes containing many smallholders (*29*). This means that some services (e.g., carbon sequestration) might be most easily provided by large industrial plantations rather than by many small farmers. Such a market might then displace smaller farmers and thus generate significant social costs.

Forest Landscape Restoration

Most degraded tropical landscapes are a mosaic of land uses and may include patches of intact residual forest and productive agricultural lands as well as degraded lands. It is rarely possible to reforest the whole landscape, especially if it is also occupied by many small farms. Under these circumstances, forest restoration is usually done by concentrating on particular sites. These might be riparian areas, buffer zones around residual forest patches, corridors between forest areas, eroding areas on steep hills, etc. However, the effectiveness of conserving biodiversity and restoring key ecological functions that operate at landscape scales (e.g., stabilizing hillslopes and hydrological processes) depends on these separately restored sites complementing others in the landscape mosaic. Individual decisions made by many small landholders are unlikely to achieve this optimal outcome. This then prompts questions such as which parts of the landscape should be reforested first, what type of reforestation should be carried out in particular

locations, and what proportion of the landscape should be reforested to achieve particular objectives.

The significance of these questions is that redesigning landscape mosaics may offer greater opportunities than can be achieved at a single site for conserving biodiversity while also improving ecological functioning. That is, the trade-off between conservation and improvements in human well-being may be easier to achieve at a landscape level than at a site level (Fig. 2).

Some progress is being made to answer these questions to achieve certain biodiversity or functional outcomes. However, this still leaves the rather more difficult task for landscape restorationists of achieving these outcomes while also balancing the goals of the many stakeholders who have an interest in the landscape. Not only will these stakeholders differ in the extent to which they can or are willing to share the costs and benefits of any restoration program, but they will also differ in the size of their landholdings and in their economic and political power. In the immediate future, an opportunistic but targeted response by land management authorities aimed at key resources such as water or soil conservation may be all that is possible. In the longer term, it will be necessary to create appropriate conditions for the participation of all relevant stakeholders in the planning and implementation of restoration initiatives.

Outlook

The current rate of deforestation in tropical regions constitutes a major global biodiversity crisis. This loss of biodiversity is significant, but so too are the poverty levels of people who rely on these forests and degraded lands for their livelihoods. Both issues need to be addressed.

Conserving and actively managing the large areas of secondary forest that are now present is one way of doing this. Many rural communities are able to carry this out once appropriate government policies have been developed (*4*, *13*). But natural recovery is not always possible, and there are a variety of newer reforestation methodologies becoming available for areas that are currently deforested. A number of these have the potential to enhance biodiversity, improve ecological functioning, and improve human livelihoods. Ways must now be found of ensuring that these new land uses are made attractive to farmers and that site-specific methodologies are developed for farmers in a particular region to use.

Many hold the view that the elimination of poverty is closely linked to the conservation of biodiversity (*30*). Forest restoration for biodiversity is then a device to improve ecosystem functioning, ecological and economic resilience, and hence human livelihoods. However, the high amounts of rural poverty in some places makes it difficult to target all of these goals immediately; many smallholders may be unable or unwilling to do anything other than try to improve their immediate financial circumstances by improving agricultural productivity. But several trends suggest there may be increasing opportunities in the future to integrate agriculture and tree growing. One is the drift of populations from country to cities, which appears to be widespread in many tropical countries. Another is the likely improvements in the markets for high-quality timbers and other goods and services as supplies from natural forests decline (*27*). If more land becomes available and markets for forest products and services improve, there will be even more scope for making restoration and conservation contribute to poverty reduction.

The biggest challenge, however, will be moving restoration from a site-based activity to a landscape activity. It is at the landscape level that restoration can be used to complement the existing protected area network, and it is at the landscape level that biodiversity restoration and production (and hence poverty alleviation) can be most easily made complementary.

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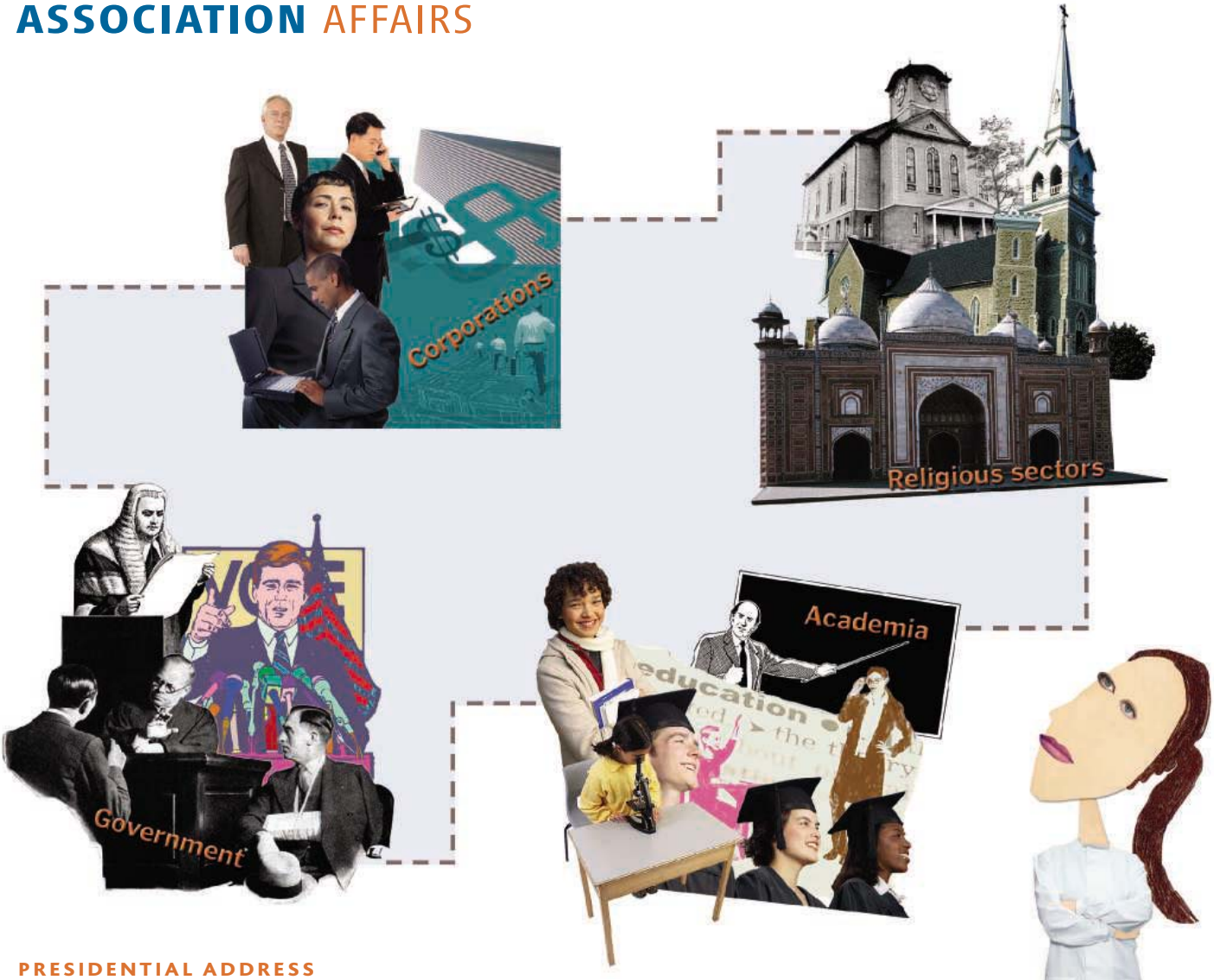

PRESIDENTIAL ADDRESS

The Nexus: Where Science Meets Society

Shirley Ann Jackson

"The nexus of science and society" is a phrase that can be interpreted in multiple ways. As participants in this meeting, some of you may have been asking yourselves: How, exactly, was this theme derived? Does the "nexus" refer to the manner in which scientific advances address fundamental human needs? Does it refer to the role scientists, themselves, play in various sectors of society, as researchers, discoverers, inventors, educators, government leaders, lobbyists, and concerned citizens?

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Could this nexus refer to the cross-disciplinary, multisector partnerships that synergize our best scientific innovation? Or is it the impact that science exerts on other aspects of society, such as national security, economic prosperity, health care, and the overall quality of life? Is not the real nexus simply the way in which scientific viewpoints influence the public policy debate?"

The answer, of course, is yes. That is precisely what is meant. The nexus is all these ideas, rolled into one.

The role that science and scientists play in society—the degree of influence wielded by scientific opinion, the reputation of scientific bodies for impartially rendered insight, the priority accorded to scientific research and education—has been vital to our success as a nation, nearly on a par with our democratic principles and ethical precepts.

Now let me remind you of what you already know: that the frontiers of science have never looked more promising than they do today. Opportunities abound. From nanotechnology, to bioengineering, to terahertz imaging, to string theory, to space science, we are in an age of discovery and innovation. The challenge is how to mine these opportunities for all they are worth to improve human health and welfare and security and to have greater public understanding of, and respect and appreciation for, science.

The Place of the Scientist in the Agora: A Metaphor

To frame these ideas, I would like to introduce the simple metaphor of what the ancient Greeks would have called the agora. This represents the place where, historically, interactions occur among societal sectors and the public at large. The government occupies a quadrant (the decision-makers, the legislators, the bureaucrats, the regulators, the courts, and the body of law itself). Industry and the private economic sector (from merchants to corporations) hold their share of real estate. The religious sector (church, mosque, synagogue, and temple) has its place in the agora. And, last but not least, academia: the educators and students who shape the future. The agora is the societal nexus.

This agora is where the public selects its "truth"; or, put differently, what society will accept as "fact." This is where leaders make public policy decisions. But what is the role played by science? Where does the scientist stand in this arena? And how does the role of the scientist shape the formation of public policy? It is instructive to consider how the role of science has changed as civilization has evolved. In primitive society, the agora, as I have described it, did not yet exist. Science and religion were frequently merged in a single figure: a medicine man or wise woman. Government, as such, was either vested in this authority figure or subject to it in terms of decision-making. Scientific knowledge was passed on by word of mouth to a select few, and breakthroughs occurred by accident, if at all. In this model, substantial improvements to the quality of life were achieved very slowly, sometimes over millennia.

In the Renaissance, science began to emerge as an authority in its own right. Discovery and invention were cause for delight. By the time Francis Bacon wrote *The Advancement of Learning* in 1605, he and others were ready to suggest a split in jurisdiction between divine philosophy and natural philosophy. While the Church retained its influence over the former, disciplines that had their roots in nature and could be verified empirically (such as navigational astronomy, optics, and medicine) became the province of reason and science. By the time Bacon published *Novum Organum* in 1620, he was ready to lay out the principles of the scientific method. What followed, logically enough, were the Age of Reason and the Industrial Revolution. In the Industrial Revolution, the search for knowledge—the focus of scientific inquiry and engineering invention—frequently was determined by economic necessity; in other words, the direction of science followed emerging societal needs.

What I would have you consider next is science in the United States in the past half century, dominated by what some refer to as the Vannevar Bush model. A key assumption of this model was that of multisector partnership in scientific endeavors, especially between the government and universities. The core of this approach—government investment in basic research in universities—had three key embedded ideas. First, that basic research would lead to innovations which, in turn, would be exploitable for national security, economic growth, and sustained societal benefit. Second, that although the source of the next discovery could not be predicted, broad-based research investments gave confidence that such discoveries would arise. And third, a concomitant investment would be made in the development of human capital in science and technology, coupled to the support of the research itself.

> The AGORA is where the public selects its "truth"; or, put differently, what society will accept as "fact." . . . Where does the scientist stand in this arena?

In the United States, the initial payoff of this model—the specific broad-based utilization of scientific talent for national needs—was realized in terms of winning World War II. The war was won on the talents of scientists and engineers, whose work gave the nation weapons systems, radar, infrared detection, bombers, long-range rockets, and torpedoes. This was primarily the result of the use of immigrant talent developed in European universities and less the result of U.S. investment in developing it, but the point was made.

After the launch of Sputnik by the Soviets, there was an acceleration of investment in science and engineering research and human capital development, leading to U.S. dominance in the arms race and the space race and to advances in energy, health, transportation, and other sectors, in ways that could not have been foreseen when the original investment was made. For instance, when the transistor was invented in 1947, it was thought only that the device might lead to better hearing aids. Instead, as you know, transistors are essential to almost every system or electronic device manufactured today, from computers and cameras to spacecraft and missiles.

The Vannevar Bush model created an environment in which the United States dominated global science and engineering research and innovation for more than five decades. In fact, economists estimate that as much as half of U.S. economic growth over the past half century has been due to advances in science and technology. Consider air transportation, atomic energy, jet and rocket propulsion, other space technologies, communications, television, computers, semiconductors, microchips, laser optics, and fiber optics: developments that have revolutionized life and spawned new industries.

Key Trends of Recent Decades

Before we attempt to diagram the agora of our time—the early 21st century—it is important to understand the convergence of a number of key trends.

Multidisciplinarity. One is embedded in science and engineering research itself. Consider the rise of nanotechnology. If someone asked you to design more effective armor for soldiers, would you begin by studying the manipulation of matter at the molecular level? Probably not. And yet, researchers in nanotechnology (the practice of manipulating matter at the atomic or molecular level) have made great strides toward developing strong protective clothing for soldiers, in the form of "dynamic armor" that can be activated quickly on the battlefield.

In another example, scientists at Johns Hopkins University have developed a self-assembling protein gel that stimulates biological signals to quicken the growth of cells. Using a combination of cells, engineered materials, and biochemical factors, the gel can replace, repair, or regenerate damaged tissues.

Pharmaceutical research has given us the "animal on a chip." Combining nanotechnology, microfluidics, and biological materials, the "animal on a chip" can reproduce the effects of chemical compounds in the human body. The application of information technology for mathematical modeling and the simulation of chemical reactions in the body, the use of combinatorial chemistry for potential drug identification, and the ability to do accelerated and efficient screening with high-throughput processes will allow faster analysis, shortened time to market, and substantially lower development costs for new pharmaceuticals. So there exists a nexus inherent in the multidisciplinarity of much fundamental and applied research.

Globalization and national security. A second key trend is globalization. The ease of global travel and satellite communication; the interlinkage of financial systems; the constant movement of merchandise, ideas, and technological know-how; and the elec-

tronic exchange of information through the Internet (in itself another synergistic innovation) have morphed the agora into a global forum of ideas. Interdependence among nations and cultures is more complex than at any other time in history.

This interdependence has both positive and negative aspects. It brings us enhanced awareness and understanding of global needs, and a greater appreciation of our shared objectives, but it also brings security risks and facilitates the unchecked movement of terrorists and illicit activity. The recent efforts of the International Atomic Energy Agency to uncover the nuclear weapons technology network of A. Q. Khan and his associates illustrate, dramatically, the vulnerabilities that have come with globalization.

One direct consequence of our heightened security awareness is that technological advances, now more than ever, are being evaluated and funded on the basis of their security applicability: what might be referred to as a "need-based exploitation" of discovery and innovation. Examples would include the search for foolproof biometrics to safeguard against identity theft, or the use of "hyperspectral imaging" or intricate facial-feature databases to track terrorists or other criminals.

It is natural that, as a country at war, the United States has been focused on making the greatest investments in the areas of most immediate vulnerability and increasing homeland security. These actions, however necessary, have also been costly, and our focus on these immediate priorities may have been at the expense of other, more subtle aspects of security.

As we look to maintain and strengthen our own security, capacity, and sustainability, we must realize their linkages to global security, capacity, and sustainability. Although we are a small fraction of the world's population (about 5%), we are by far its greatest consumer of natural resources. This situation cannot last forever. We are very rich. The larger world is still very poor. Other nations (some emulating our model, others not) expect to improve their standards of living, as they should. We are globally linked. The scientific community has always been linked through scientist-to-scientist contact. But, as a community, we have not always looked, as we should, at the broader, direct role of science and the scientific community in solving global sustainability and human health and welfare issues. This requires broadening our focus, entering the policy debates as they apply, globally, and having our professional institutions focus in this way.

A primary challenge of the developed world is to deal with terrorism and destabilization by dealing with their causes, primarily in the Third World. Fundamental research and the innovations that derive from it give us a way to do this directly, with benefits accruing to all, particularly as they relate to food, health, infrastructure, and environment. Some examples include food, especially genetically engineered, insect-resistant crops; health, especially new medicines and new disease treatment modalities; infrastructure and environment, including new engineering solutions for clean water and sustainability; and, of course, energy. No nation can grow and prosper economically without addressing these needs. Science and engineering can be a potent force for security in this positive sense. This is the nexus where science meets society in global terms.

As we look to maintain and strengthen our OWN SECURITY, capacity, and sustainability, we must realize their linkages to GLOBAL SECURITY, capacity, and sustainability.

Workforce and education trends. Another subtle aspect of security relates to human capital development. Before the attacks of September 11, 2001, when the Hart-Rudman Commission released its "Road Map for National Security," one of its five recommendations was "recapitalizing America's strengths in science and education." The commission said that although we have enjoyed the economic and security benefits of previous investments in science and education, we have now crossed a line and are "consuming capital." This trend, the commission declared, posed "a greater threat to U.S. national security over the next quarter century than any potential conventional war that we might imagine."

What is the threat? There are four, actually. First, our scientific and engineering workforce is aging. Half of our scientists and engineers are at least 40 years old, and the average age is rising. As a recent National Science Foundation survey states, "the total number of retirements among science and engineering-degreed workers will dramatically increase over the next 20 years." In fact, the number of U.S. scientists and engineers reaching retirement age is expected to triple in the next decade. As an example, the Department of Defense expects attrition in its laboratories of 213,000 science, mathematics, engineering, and technology workers in the next 10 years. It reports, likewise, that the number of top-secret "clearable" students pursuing defense-related critical skills degrees is declining. The department projects a demand for science and engineering workers to be up 10% in 5 years, by 2010, and expects tough competition for these workers from industry. Speaking of industry, in the aerospace industry, 27% of workers are eligible to retire in 3 years.

Second, world events and resulting adjustments in federal immigration policy have made the United States less attractive to international students and scientists, long a source of talent that has augmented our own. Since 2001, visa applications from international students and scientists have fallen. Faced with new hurdles, students from other nations are choosing to study elsewhere. The number of international students on U.S. campuses declined in fiscal year 2003 by 2.4%—the first drop in 32 years. There was a 28% decline in the number of applications from abroad to U.S. graduate schools, overall, between 2003 and 2004, and a 36% decline in the number of applications from abroad to U.S. graduate engineering programs in the same time period. The decline of graduate applications from India was 28% and from China 45%.

Third, immigrants make up nearly 40% of U.S. science and engineering workers with doctoral degrees (30% of master's degrees). However, the countries that have been primary sources of science and engineering talent for the United States in recent times (China, India, Taiwan, and South

Korea) are making a concerted effort to educate more of their own at home and to fund more research within their borders. Between 1986 and 1999, the number of science and engineering doctorates granted increased 400% in South Korea, 500% in Taiwan, and 5400% (that is correct—5400%) in China. Not surprisingly, the number of South Korean, Taiwanese, and Chinese students receiving doctorates in the United States declined in the late 1990s. During the decade from 1991 to 2001, while U.S. spending on research and development was rising about 60%, spending rose more than 300% in South Korea and about 500% in China, albeit from an initially much smaller base. In addition, improving global economies are offering young scientists from these and other countries more job options at home or in other nations. In short, the image of America as the land of opportunity, though still a bright vision, may be losing some of its luster in terms of both educational and career opportunities.

To complete this part of the picture, I also should mention the trend toward global research and development for multinational corporations. What began as a move of U.S. manufacturing bases to produce goods in countries with cheaper labor costs has, in recent years, shifted to include more high-technology jobs, to be where new markets are and where there are well-educated workforces. The present trend is for U.S. (as well as Japanese and Western European) companies with sufficient funds and infrastructure to establish research and development operations in China, India, and other countries where the skilled human capital is available.

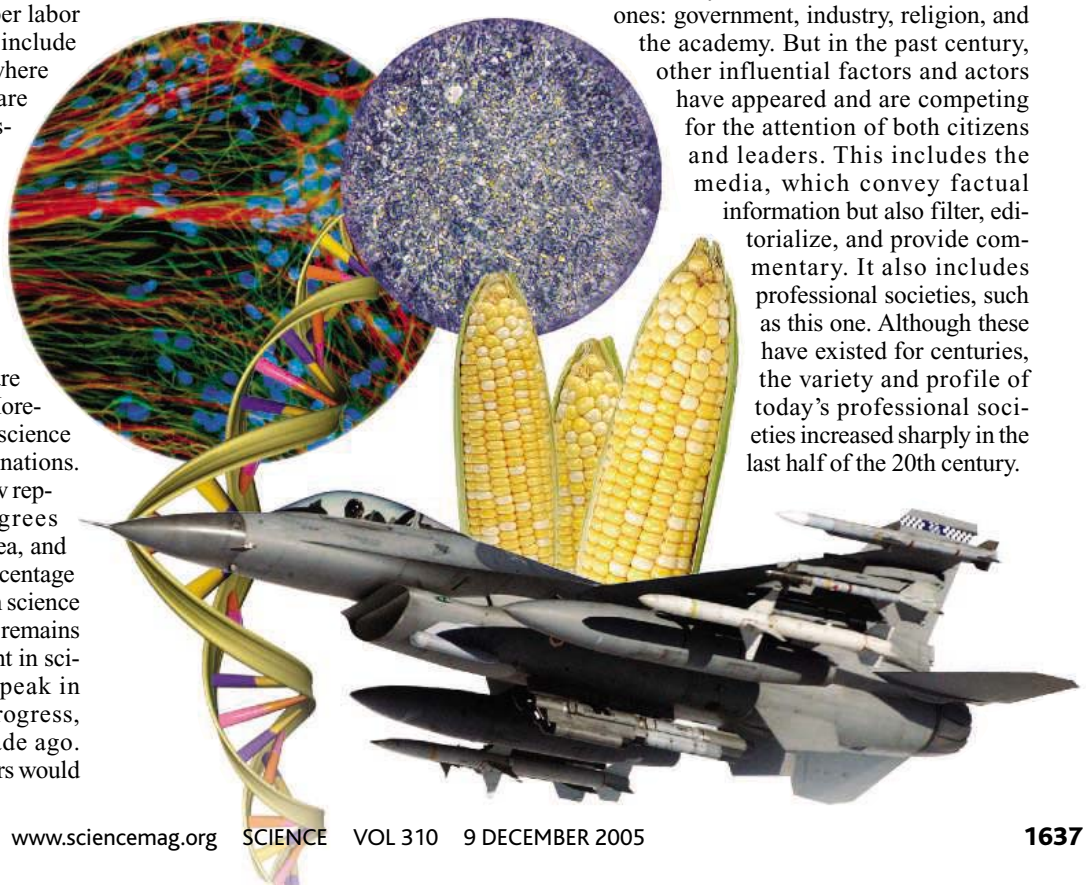
Fourth, fewer young Americans are studying science and engineering. Moreover, the proportional emphasis on science and engineering is greater in other nations. Science and engineering degrees now represent 60% of all bachelor's degrees earned in China, 33% in South Korea, and 41% in Taiwan. By contrast, the percentage of those taking a bachelor's degree in science and engineering in the United States remains at roughly 31%. Graduate enrollment in science and engineering reached a peak in 1993, and despite some recent progress, remains below the level of a decade ago. Individually, each of these four factors would be problematic. In combination, they could be devastating.

So we are at a critical juncture. The war on terror, the uneven economic expansion of the recent past, and the U.S. federal budget deficit have weakened U.S. government resolve to invest in basic research and the development of scientific talent. This is happening just when we should be investing more, not less. A true story gives a lesson. As a Cold War continuation of the national defense effort, the Rand Corporation engaged in basic super-secret research. During summers of the early 1950s, a young and somewhat peculiar mathematician from Princeton University joined their ranks. The work of John Forbes Nash on "game theory" would become the most influential theory of rational human behavior, ultimately revolutionizing the field of economics. The work won Nash a Nobel Prize in Economics in 1994. Game theory opened alternative ways of thinking and analysis. It gave the government a new way to sell access to public resources through auctions—oil leases, T bills, timber, pollution rights—to corporations and conglomerates, which develop them. Early in his career, Nash succumbed to schizophrenia, recovering miraculously three decades later. His story is told in the book *A Beautiful Mind*, by Sylvia Nasar, later made into a movie. His story is filled with individuals and institutions that accepted his unique diversity and made every effort to enable him to continue to work.

On issues ranging from GENETIC ENGINEERING and STEM CELL RESEARCH to the search for WEAPONS of MASS DESTRUCTION, our public discourse abounds with controversy, and the volume and passion of the rhetoric sometimes DROWN the VOICE of SCIENCE itself.

The Institute for Advanced Study at Princeton itself presents another interesting lesson. In the 1930s and 1940s, when other universities declined to offer positions to Jewish refugee scientists and mathematicians fleeing Nazi Germany, the institute opened its doors. The result was a constellation of brilliance at the Institute for Advanced Study at Princeton, anchored by Albert Einstein, whose "miracle year" we celebrate at this meeting as part of the World Year of Physics. The lesson of the Institute for Advanced Study at Princeton during the Einstein period and of John Forbes Nash at Princeton University is that talent resides in many places—sometimes unappreciated or underappreciated. The group (or individual) that a society may ignore or neglect may be the very group (or individual) that makes the greatest discoveries or achieves the greatest innovations. We have made such mistakes in the past. We should not make them again.

Multiple voices. The final set of trends I would cite relates to the exponential rise in the volume and availability of information and how that has influenced the role of the scientist and the formation of public policy. In introducing the metaphor of the agora, I restricted my list of its residents to four basic ones: government, industry, religion, and the academy. But in the past century, other influential factors and actors have appeared and are competing for the attention of both citizens and leaders. This includes the media, which convey factual information but also filter, editorialize, and provide commentary. It also includes professional societies, such as this one. Although these have existed for centuries, the variety and profile of today's professional societies increased sharply in the last half of the 20th century.



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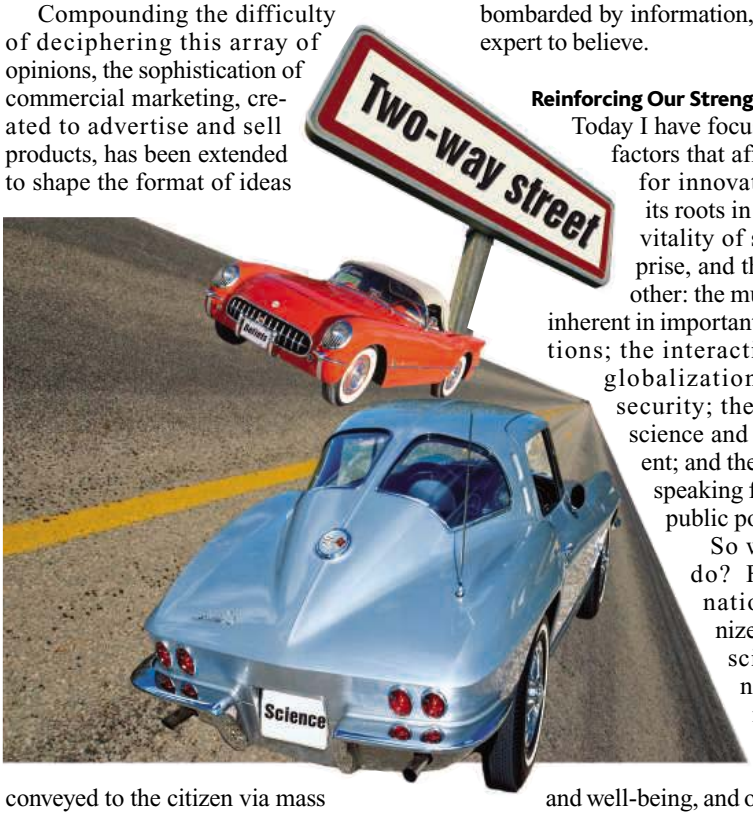
Think tanks are another factor in the mix. In the 1970s, when think tanks began to emerge, they focused generally on achieving a specific purpose or analyzing a particular social issue, and the results would be presented in a book or at a conference. Today, here in Washington, the number of think tanks has grown to more than 200; the budgets of the largest organizations are in the tens of millions of dollars; and the hundreds of experts they employ flood the forum with journals, op-ed commentaries, and television and radio appearances on every aspect of public affairs, from crop subsidies to urban renewal to matters of ethical and moral choice.

Compounding the difficulty of deciphering this array of opinions, the sophistication of commercial marketing, created to advertise and sell products, has been extended to shape the format of ideas conveyed to the citizen via mass communication media. And finally we have the Internet: an engine of information and disinformation without equal. Global in its reach, staggering in its power, it is transforming the Age of Information.



What happens when the marketplace is populated with self-proclaimed experts? When we have instantly available authorities to support every view? The result is the devaluing of information and even the devaluing of science. This trend threatens the concept of the scientist as the dispassionate, objective voice of reason, as well as the authoritative role of science in helping to shape sound public policy.

A Nexus of Distrust?

How does the public choose its truth? How does society settle on what it will accept as fact? How do our leaders, our elected officials, arrive at useful decisions? What happens to the truth-tellers: the individuals who speak out with facts that may run counter to the prevailing view? And—crucially—with what degree of trust does the average citizen regard the voice of scientific expertise? Is the voice heard?

On issues ranging from genetic engineering and stem cell research to the search for weapons of mass destruction, our public discourse abounds with controversy, and the volume and passion of the rhetoric sometimes drown the voice of science itself. What should be evident is that the nexus of science and society is increasingly an interaction prone to confusion and distrust. The citizen, bombarded by information, is unsure which expert to believe.

Reinforcing Our Strengths

Today I have focused primarily on factors that affect the capacity for innovation, which has its roots in the strength and vitality of scientific enterprise, and that play off each other: the multidisciplinarity inherent in important scientific questions; the interaction of science, globalization, and national security; the availability of science and engineering talent; and the multiple voices speaking for science in the public policy arena.

So what should we do? First, we as a nation must recognize the centrality of science and engineering for our national security, our economic health and well-being, and our ability to help alleviate human suffering worldwide. This means we need a full-fledged national commitment to invest significantly, competitively, and deeply in basic research in science and engineering across a broad disciplinary front, even in the face of competing priorities. It is stunning when people say that science is just another special interest group, because science (and technology) is the root of our success, but it is so embedded that it is taken entirely for granted.

Second, we must have a national focus and commitment to develop the complete talent pool: to reignite the interest in science and mathematics of all of our young people and to identify, nurture, mentor, and support the talent that resides in our new majority: the underrepresented majority population of women and ethnic minorities. This requires a focus on early education and preparation, especially in mathematics. But how do we encourage talented students to commit themselves to the sciences as early as middle school? To stay the often difficult course through high school? To find the means to attend the university and continue through postgraduate work? To transition into the workplace, the laboratory, the design studio?

Some incentives necessarily must be financial. This would require more economic support for students and support for a broader socioeconomic range of students, of all ethnic backgrounds and at all educational levels, through graduate school. An example, as others have suggested, could be patterned on portable fellowships like those once offered as a result of the National Defense Education Act for graduate study in science and engineering.

Third, the scientific community must engage on key public policy issues in a consistent and pro-active, not reactive, way. Public policy is not always (perhaps not often) an ideal forum for fair debate. It is a roiling marketplace where every voice has its own agenda and where an issue can become veiled and confused. But it is a public marketplace for ideas, it is democratic, and it is open. Of course, the public and our political leaders must be willing to listen. There needs to be greater awareness and greater respect for scientists and the role of science in resolving critical national and international issues.

The nexus of science and society is not always comfortable for scientists or for the public at large. But because public institutions largely fund basic research and support the training of students, science and public policy (even politics) are joined. We need to look not only at the technical dimensions of public policy but at the policy dimensions of technological change that springs from basic science.

An example of the nexus of science, technology, and public policy is in the use of risk assessment in the nuclear arena. I was chairman of the U.S. Nuclear Regulatory Commission (NRC) from 1995 to 1999. It is the responsibility of the NRC to ensure safety in the design, construction, and operation of nuclear power plants, and, in so doing, to protect the public and the environment and to preserve national security. The NRC's historical approach to this had been prescriptive, with fixed rules. The public gained comfort when all the rules were strictly enforced, even if the safety basis of the rules was not clearly understood. This sometimes leads to public overreaction to events in nuclear power plants, because of an inability to distinguish significant from nonsignificant events.

Beginning in the 1970s, probabilistic risk assessment was developed as a quantitative

way in which to balance the risks of nuclear operations. It was slowly adopted by the NRC and the nuclear industry. But from the mid-1990s forward, that adoption was accelerated. The regulatory framework began moving from prescriptive to risk-informed, meaning a more robust use of probabilistic risk assessment to inform, but not absolutely determine, all regulatory functions and requirements. Science, then, informed but did not determine regulatory policy. But what remains to be done, even today, is to move from risk-informed regulation to helping the public understand how risks are evaluated and balanced, in the nuclear reactor arena as well as in the nuclear waste arena.

Science and technology might suggest that one way of disposing of spent nuclear fuel is to reprocess it, extract plutonium, make MOX fuel, and burn it in nuclear power plants to gain greater efficiency and to meet nonproliferation goals by burning up excess plutonium. This is routine in other nations. But the policy of the U.S. government since the 1970s has been not to separate plutonium through reprocessing, because of proliferation risk, and instead to opt for geologic disposal, with plutonium embedded in a toxic residual fission product matrix. Science can speak to the risks and energy efficiency of one approach or the other, but which way to go is a public policy decision. Science can inform the policy debate but not totally control its outcomes.

Fast forward to today. Terrorism and national security are top-of-the-mind issues in this country and are of concern worldwide. There are various technologies, as mentioned earlier, being used to identify and to track potential terrorists. The public, especially in the United States, has a general feeling of unease, while some worry about the effect of security measures on civil liberties, and others worry about the scientific community itself—about the ease of communication and interaction with scientists worldwide for the advance of science. What is not clear is how much of a comprehensive risk assessment approach to current vulnerabilities exists. This is where the scientific community can play a much-needed role and can contribute to a more open discussion, not of terrorist targets or specifically how risk assessment is used, but at least that it is used. We cannot protect against everything. But we can use risk assessment to deploy resources in an efficacious way, to track the right things, to aggravate people less, and to calm unnecessary public fears.

Fourth, we must engage the public and make science more accessible to all. That is why the AAAS outreach efforts should be more strongly replicated by other, more discipline-specific scientific and engineering professional societies. It is important that the scientific community, in its outreach, help people not only to see the fun of science but also to understand what science is, what a scientific theory is (as opposed to a belief), how science is done, that accepted scientific models or theories are based on evidence, that hypotheses are tested by experiment, and that theories change as new evidence emerges.

We must address the ethics of the application of SCIENCE in key areas and how it ties into people's core BELIEFS. It is a TWO-WAY STREET that needs to be traveled more frequently.

This is important in overcoming mistrust of science and scientists and the movement away from understanding the importance of science to modern life, of its role in addressing issues of human health and welfare. We must address the ethics of the application of science in key areas and how it ties into people's core beliefs. It is a two-way street that needs to be traveled more frequently. It also will help to bring light—and less heat—to issues such as evolution versus intelligent design: the one a scientific theory rooted in experimental results, the other not. What this really means is that the scientific community must understand that the nexus of science and public policy inherently means its nexus with public values. We must meet people where they live. Scientific perspectives will not prevail in all arenas, at all times, but we must engage nonetheless.

Summary

More than half a century of U.S. dominance in science and engineering research has both engendered and been driven by a number of unique advantages, which we should identify, retain, and reinforce. They include (i) the most extensive and sophisticated system of higher learning in the world; (ii) a financial system that provides ready access to venture capital and has a long tradition of investment in entrepreneurial projects; (iii) government structures designed to support the scientific enterprise, and government policies that encourage entrepreneurship; (iv) a history and tradition of collaboration between the public and private sectors; and (v) a culture of risk-takers, in which divergent ideas and viewpoints are sought out and welcomed, with the confidence and creativity to achieve innovation.

If we take these advantages and continue to invest in science and engineering research across a range of disciplines, develop our human capital (accessing the complete talent pool), engage on key public policy issues actively and consistently, and engage the public in new, creative, and respectful ways, we can heal rifts, address rising expectations worldwide, ensure our security by helping others to feel secure, and usher in a new "golden age" of scientific discovery.

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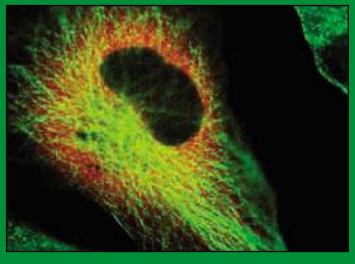

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Increase in Activity During Calorie Restriction Requires Sirt1

Danica Chen,[1] Andrew D. Steele,[1,2] Susan Lindquist,[2] Leonard Guarente[1]*

Sir2 (silent information regulator 2) is a nicotinamide adenine dinucleotide (NAD)–dependent deacetylase that is required for longevity due to calorie restriction in the budding yeast *Saccharomyces cerevisiae* and in the fruit fly *Drosophila melanogaster* (*1*, *2*). In mammals, calorie restriction induces a complex pattern of physiological and behavioral changes, such as a reduction in blood glucose, triglycerides, and growth factors, and an increase in movement and foraging activity (*3*–*6*). Here we report that the mammalian Sir2 ortholog, Sirt1, is required for one of these phenotypes, the increase in physical activity.

To address a possible role in calorie restriction for Sirt1, we measured the food intake of wild-type and knockout (KO) mice lacking functional Sirt1 that were fed ad libitum [wild type: 4.26 ± 0.43 grams of chow per day (g/day); KO: 4.08 ± 0.72 g/day chow]. The food allotment for all the restricted mice was adjusted to 60% of the ad libitum values, and food was administered once daily.

Consistent with earlier reports, we observed a large increase in physical activity in wild-type mice after 9 months of calorie restriction (*4*–*6*). Five separate measurements of movement in the home cage—distance traveled, hanging in a cuddled position, hanging in a vertical position, jumping, and walking—showed this increase (Fig. 1A). We observed either no increase or greatly reduced increases in these activities in the knockout mice on the calorie-restriction regimen. We also determined motor capacity in wild-type and knockout mice by measuring their ability to stay on an accelerating treadmill or rotarod. The knockout mice performed better than wild-type mice in these assays (Fig. 1B), suggesting that the failure of the knockout mice to increase their physical activity during calorie restriction was not caused by a reduced capacity for movement.

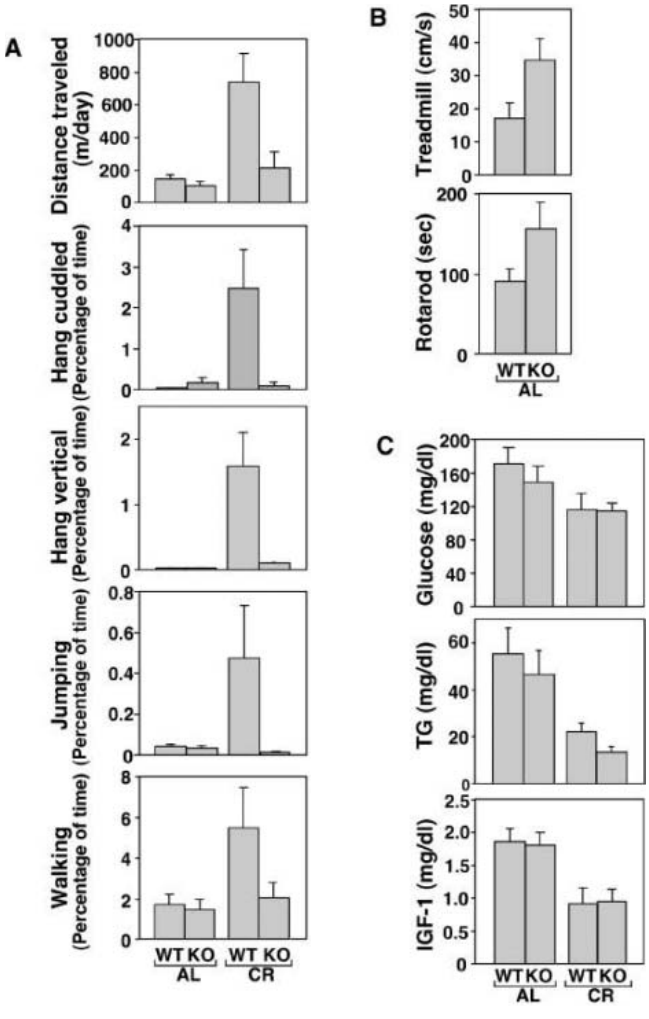

Fig. 1. The physiological and behavioral changes of calorie restriction in wild-type and Sirt1 knockout mice. (**A**) Calorie restriction increases physical activity of wild-type (WT) but not Sirt1 knockout (KO) mice. Five parameters of movement were recorded of Sirt1 knockout and wild-type mice fed ad libitum (AL) or calorie restricted (CR). (**B**) Sirt1 knockout mice do not have reduced movement. The motor capacity of mice was tested in treadmill and rotarod assays. (**C**) Calorie restriciton induces comparable physiological changes in wild-type and knockout mice. Blood glucose, TG, and IGF1 were reduced comparably by calorie restriction in wild-type and knockout mice. Body weights were also reduced by calorie restriction [37.8 ± 3.8 g (AL) to 19.9 ± 1.9 g (CR) for WT mice; 18.29 ± 2.7 g (AL) to 15.4 ± 1.4 g (CR) for KO mice].

The inability of knockout mice to respond to calorie restriction was also not due to them experiencing a lower degree of food restriction. Serum levels of glucose, triglycerides (TG), and insulin-like growth factor 1 (IGF1) were reduced comparably in both wild-type and knockout mice (Fig. 1C), indicating that the regimen exerted expected effects on these physiological parameters and that Sirt1 was not required for these changes.

Our findings suggest that a parameter of mammalian calorie restriction, up-regulation of physical activity, requires the gene that codes for Sirt1. The molecular mechanism for this increase in physical activity is not known. It is possible that calorie restriction triggers changes in brain regions that govern physical activity and that Sirt1 is a regulator of this pathway. It will be of interest to determine whether Sirt1 mediates other effects of calorie restriction in mammals, such as the extension of life span.

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The Kinase LKB1 Mediates Glucose Homeostasis in Liver and Therapeutic Effects of Metformin

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The Peutz-Jegher syndrome tumor-suppressor gene encodes a protein-threonine kinase, LKB1, which phosphorylates and activates AMPK [adenosine monophosphate (AMP)–activated protein kinase]. The deletion of LKB1 in the liver of adult mice resulted in a nearly complete loss of AMPK activity. Loss of LKB1 function resulted in hyperglycemia with increased gluconeogenic and lipogenic gene expression. In LKB1-deficient livers, TORC2, a transcriptional coactivator of CREB (cAMP response element–binding protein), was dephosphorylated and entered the nucleus, driving the expression of peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α), which in turn drives gluconeogenesis. Adenoviral small hairpin RNA (shRNA) for TORC2 reduced PGC-1α expression and normalized blood glucose levels in mice with deleted liver LKB1, indicating that TORC2 is a critical target of LKB1/AMPK signals in the regulation of gluconeogenesis. Finally, we show that metformin, one of the most widely prescribed type 2 diabetes therapeutics, requires LKB1 in the liver to lower blood glucose levels.

Introduction. The adenosine monophosphate–activated protein kinase (AMPK) is a conserved regulator of the cellular response to low energy, and it is activated when intracellular adenosine triphosphate (ATP) concentrations decrease and AMP concentrations increase in response to nutrient deprivation and pathological stresses (*1*). In budding yeast, the AMPK homolog Snf1 is activated in response to glucose limitation. In mammals, AMPK has a critical role in many metabolic processes, including glucose uptake and fatty acid oxidation in muscle, fatty acid synthesis and gluconeogenesis in the liver, and the regulation of food intake in the hypothalamus (*1–4*). AMPK exists as a heterotrimer, composed of the catalytic kinase α subunit and two associated regulatory subunits, β and γ (*1*). Upon energy stress, AMP directly binds to tandem repeats of crystathionine-β synthase (CBS) domains in the AMPK γ subunit, causing a conformation change that exposes the activation loop in the α subunit, allowing it to be phosphorylated by an upstream kinase (*1*). The sequence flanking the critical activation loop threonine (Thr^{172} in human AMPKα) is conserved across species, and its phosphorylation is absolutely required for AMPK activation.

Three papers (*5–7*) recently reported that the kinase LKB1 is biochemically sufficient to activate AMPK in vitro and is genetically required for AMPK activation by energy stress in a number of mammalian cell lines. Because of this potent connection to AMPK, we began to consider the possibility that LKB1 might normally function as a central regulator of organismal metabolism. In the liver, AMPK is regulated in response to adipokines such as adiponectin and resistin, which serve to stimulate and inhibit AMPK activation, respectively (*8*, *9*). Exercise and several current diabetes therapeutics activate AMPK in muscle and in liver and are thought to therapeutically act in part through stimulation of this pathway in those tissues (*10–16*). However, Ca^{2+} calmodulin-dependent protein kinase kinase β (CAMKKβ) also activates AMPK (*14–16*). CAMKKβ phosphorylates and activates AMPK in response to calcium, whereas LKB1 appears to be responsible for regulating AMPK under energy stress conditions that involve the accumulation of intracellular AMP (*17–20*). Moreover, in budding yeast, there are three AMPK kinases (AMPKKs) that are functionally redundant, and all three contribute to metabolic regulation (*21–24*). Therefore, it was unclear whether LKB1, CAMKKβ, or another AMPKK might regulate AMPK activity in critical metabolic tissues in mammals. We genetically deleted LKB1 in adult mouse liver and examined its role in AMPK activation and the effect of the loss of this pathway on glucose homeostasis. We also examined the therapeutic response to metformin, which is a drug widely used to lower blood glucose concentrations in diabetes patients. Finally, we have defined a signaling pathway by which LKB1 regulates a specific CREB (cAMP response element–binding protein) coactivator that serves as a rate-limiting switch controlling gluconeogenesis in the liver.

LKB1 deletion in liver results in loss of AMPK activation. We generated cohorts of mice that were either wild-type for LKB1 or were homozygous for a conditional floxed allele of LKB1 (*25*) by breeding $LKB1^{lox/+}$ males to $LKB1^{lox/+}$ females. The resulting 8-week-old male mice of both $LKB1^{+/+}$ and $LKB1^{lox/lox}$ (henceforth referred to as +/+ and L/L, respectively) genotypes were tail-vein injected with adenovirus expressing Cre recombinase from the cytomegalovirus (CMV) promoter (*26*). Because of the high tropism of adenovirus for hepatocytes (*27*), we observed >95% deletion of LKB1 protein in the livers of the L/L, but not +/+, animals injected with adenovirus Cre, with no signs of deletion in muscle, pancreas, or spleen tissue, as judged by immunoblotting of proteins from lysates of these tissues (Fig. 1A and fig. S2). We expect that only hepatocytes are susceptible to adenoviral infection, and the failure to observe 100% deletion of LKB1 in total tissue extracts from liver may reflect the presence of supporting endothelial and stromal cells in this tissue.

We examined the activation of AMPK using an antibody specific for AMPK that is phosphorylated on Thr^{172}, the critical threonine in the activation loop of AMPK that is phosphorylated by LKB1 (*5*, *7*). The deletion of LKB1 in the liver resulted in a proportional decrease of AMPK phosphorylation at Thr^{172}, suggesting that in this tissue, LKB1 accounts for most of the phos-

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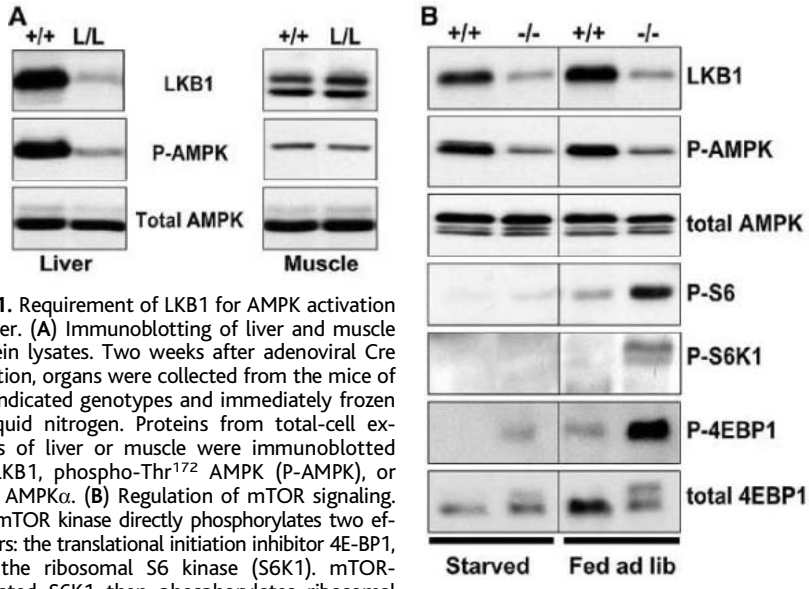

Fig. 1. Requirement of LKB1 for AMPK activation in liver. (**A**) Immunoblotting of liver and muscle protein lysates. Two weeks after adenoviral Cre injection, organs were collected from the mice of the indicated genotypes and immediately frozen in liquid nitrogen. Proteins from total-cell extracts of liver or muscle were immunoblotted for LKB1, phospho-Thr^{172} AMPK (P-AMPK), or total AMPKα. (**B**) Regulation of mTOR signaling. The mTOR kinase directly phosphorylates two effectors: the translational initiation inhibitor 4E-BP1, and the ribosomal S6 kinase (S6K1). mTOR-activated S6K1 then phosphorylates ribosomal S6. Thus, the level of phosphorylation of 4EBP1, S6K1, and S6 reflect the level of mTOR activation within the cell. Two weeks after adenoviral Cre injection, mice of the indicated genotypes were fasted for 18 hours overnight or fed ad libitium (ad lib) and then killed. Total-cell extracts were made from liver or muscle and immunoblotted with indicated antibodies to examine AMPK activation and mTOR activation in wild-type and LKB1-deficient livers after an 18-hour fast or under ad lib fed conditions, as indicated.

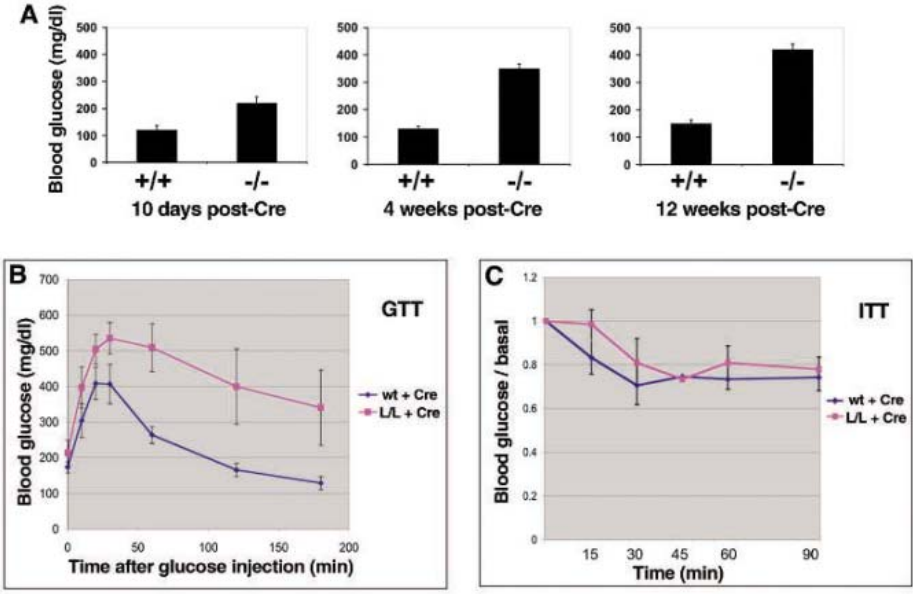

Fig. 2. Glucose homeostasis defects in mice lacking LKB1 in liver. (**A**) Mice of the indicated genotypes were fasted for 18 hours at indicated times after adenoviral Cre injection, and fasting blood glucose was measured. $P < 0.01$ at all time points. (**B**) Glucose-tolerance test (GTT) on mice of indicated genotypes 2 weeks after adenoviral Cre injection. (**C**) Insulin-tolerance test (ITT) on mice of indicated genotypes 2 weeks after adenoviral Cre injection. No significant difference was observed. Data represents the mean + SEM for six mice of each genotype. Average T0 glucose levels for the wild-type mice = 180 mg/dl; average T0 glucose levels for the L/L mice = 355 mg/dl.

phorylation of AMPK (Fig. 1A). There was no effect of LKB1 loss on the amount of total AMPKα.

One of the critical targets downstream of LKB1 and AMPK in fibroblasts and tumor cells is the mammalian target of rapamycin (mTOR) signaling pathway (*28*–*30*). In response to energy stress, AMPK is activated in an LKB1-dependent manner and phosphorylates the tuberous sclerosis complex 2 (TSC2) tumor suppressor, activating it to inhibit mTOR signaling. Loss of LKB1 in intestinal tumors from *LKB1*$^{+/-}$ mice is accompanied by an increase in mTOR signaling, as detected by the phosphorylation of two of its best-characterized targets, p70 ribosomal S6 kinase (S6K) and eukaryotic translational initiation factor (eIF) 4E binding protein 1 (4E-BP1) (*29*). Loss of LKB1 and AMPK activity in liver was also accompanied by increased phosphorylation of 4E-BP1, S6 kinase, and its substrate ribosomal S6 (Fig. 1B). We did not detect any effect of overnight fasting or feeding on the phosphorylation of AMPK. However, mTOR signaling was abolished under starvation conditions in both wild-type and LKB1$^{-/-}$ livers, suggesting that fasting does not inhibit mTOR through AMPK and that positive signals from nutrients and feeding are required to activate mTOR in the liver.

LKB1 deletion in liver causes severe hyperglycemia. AMPK controls two critical liver functions: gluconeogenesis and lipogenesis (*1*, *31*). We examined fasting blood glucose levels in littermate +/+ and L/L mice at various times after administration of Cre. Fasting blood glucose levels were high in the Cre-treated L/L mice at all time points examined, compared with those of Cre-treated wild-type littermates. Resting levels of blood glucose also increased with time (Fig. 2A). Consistent with these findings, the overexpression of a constitutively active AMPKα2 allele in the liver resulted in hypoglycemia (*31*). Mice lacking hepatic LKB1 also had impaired ability to maintain normal blood glucose concentrations after injection of glucose (Fig. 2B). However, these animals showed a normal reduction in blood glucose in response to insulin injection, suggesting that peripheral glucose uptake was not impaired in these animals (Fig. 2C).

The increase in blood glucose in mice lacking liver LKB1 was accompanied over time by compensatory increases in blood insulin levels, as expected for mice with normal pancreatic function (fig. S3). Despite these changes in blood glucose and insulin profiles, mice lacking LKB1 in the liver did not demonstrate increased body weight compared with their control littermates, even when placed on a high-fat diet for 2 months (fig. S4).

LKB1 loss results in increased gluconeogenic and lipogenic gene expression. The observed hyperglycemia in the mice lacking hepatic LKB1 may result from an inability to appropriately turn off gluconeogenesis. To study the effect of LKB1 loss on gluconeogenesis, we examined the expression of critical gluconeogenic genes by quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR). The CREB transcription factor is a critical component of the response to starvation signals and the induction of gluconeogenesis in liver (*32*). The peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α) transcrip-

tional coactivator is an essential transcriptional target of CREB in this process (*32*–*35*). Loss of PGC1α in the liver results in hypoglycemia and a decreased production of gluconeogenic enzymes. PGC1α is thought to mediate transcription downstream of the nuclear receptor hepatocyte nuclear factor 4α (HNF4α) and the transcription factor Foxo1 in the promoters of key gluconeogenic enzymes, including glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxylase (PEPCK) (fig. S5) (*33*–*39*). The expression of G6Pase and PGC1α mRNA was increased in LKB1-deficient livers, whereas no change was observed in the expression of hexokinase mRNA (Fig. 3A). We also detected increased amounts of PGC1α protein in fasting LKB1-deficient mice (Fig. 3A).

AMPK activity also inhibits lipogenesis (*11*, *31*). Amounts of mRNA encoding the critical lipogenic transcription factor sterol regulatory element–binding protein 1 (SREBP-1) were increased in LKB1-deficient livers along with those several well-described targets of SREBP-1 and the carbohydrate response element binding protein (ChREBP), which include the following: fatty acid synthase (FAS), acetyl CoA carboxylase (ACC1), and liver pyruvate kinase (L-PK) (Fig. 3B). In contrast, marginal effects were observed on transcription of the ChREBP transcription factor itself. Protein levels of FAS and ACC1 were similarly increased in LKB1-deficient livers (fig. S6).

TORC2 is deregulated in LKB1-deficient livers and drives gluconeogenesis. We found that PGC1α mRNA expression was increased, which led us to hypothesize that the activation of gluconeogenesis was occurring at a step before the transcription of gluconeogenic enzymes. The CREB coactivator TORC2 (transducer of regulated CREB activity 2) is a critical regulator of gluconeogenesis in mice (*40*). TORC2 mediates CREB-dependent transcription of PGC1α and its subsequent gluconeogenic targets PEPCK and G6Pase. TORC2 is regulated by a series of phosphorylation events, and its nuclear localization is controlled by phosphorylation of Ser^{171} (numbering for human TORC2) (*40*, *41*). Phosphorylation at this site confers binding of the protein 14-3-3 and sequestration of TORC2 out of the nucleus. The kinase responsible for phosphorylating Ser^{171} of TORC2 was initially identified as salt-inducible kinase 2 (SIK2), one of three SIKs all related to AMPK (*41*). Recently, activation of AMPK was also found to phosphorylate TORC2 and regulate cytoplasmic translocation of the coactivator in primary hepatocyte cultures (*40*). LKB1 phosphorylates and activates of a number of kinases in the AMPK kinase subfamily, including the SIK kinases (*42*), suggesting that genetic deletion of LKB1 in liver will result in the inactivation of multiple TORC2 Ser^{171} kinases.

The reintroduction of wild-type, but not catalytically inactive, LKB1 into LKB1-deficient tumor cells resulted in a mobility shift of TORC2 during electrophoresis, indicative of its phosphorylation at Ser^{171} (Fig. 4A) (*40*). We next examined whether endogenous TORC2 phosphorylation was affected in the LKB1-deficient livers. TORC2 from untreated wild-type livers was predominantly phosphorylated, whereas much of the TORC2 from LKB1-deficient liver exhibited a faster mobility, consistent with the absence of Ser^{171} phosphorylation. We also examined the localization of endogenous TORC2 by immunohistochemistry in sections from $LKB1^{+/+}$ and $LKB1^{-/-}$ livers. TORC2 was predominantly nuclear in $LKB1^{-/-}$ livers, whereas in wild-type mice, TORC2 was predominantly cytoplasmic (Fig. 4B). This dramatic localization change is consistent with Ser^{171} dephosphorylation being a rate-limiting event for TORC2 nuclear translocation in this physiological setting.

To examine whether the increased nuclear TORC2 is functionally active and responsible for increased gluconeogenesis in mice lacking LKB1 in the liver, we injected these mice with adenoviruses bearing small hairpin RNA (shRNA) for TORC2 or a control scrambled sequence. Five days after administering the shRNA adenoviruses, we examined fasting blood glucose levels and protein levels in the liver. TORC2 protein levels were reduced by more than 70% by the TORC2 shRNA but not by control shRNA. We observed a proportional loss of total PGC1α protein in the TORC2-shRNA–treated mice (Fig. 4C). The reduction of TORC2 and PGC1α protein levels was accompanied by a significant decrease in fasting blood glucose levels in the TORC2-shRNA–treated mice (Fig. 4D). Altogether, these data suggest that TORC2 is a critical downstream target of LKB1-dependent kinases in the control of gluconeogenesis.

Metformin requires hepatic LKB1 to lower blood glucose. Metformin is an oral biguanide that is one of the most widely prescribed therapeutics for type 2 diabetes worldwide (*1*, *43*). Metformin lowers blood glucose and blood lipid contents, and these effects are thought to be at least partially responsible for its therapeutic benefits. Decreased hepatic gluconeogenesis and increased glucose uptake in skeletal muscle have been proposed to explain the effects of metformin on hyperglycemia. Metformin has been suggested to act through the stimulation of AMPK in peripheral tissues. Consistent with this hypothesis, metformin treatment of hepatocytes results in decreased glucose output and decreased lipogenic gene expression, and these effects were blocked by treatment of the cells with a chemical inhibitor of AMPK or an expression of dominant negative AMPK, respectively (*11*, *44*).

We examined whether metformin treatment of mice increased AMPK activity in the liver in an LKB1-dependent manner. AMPK

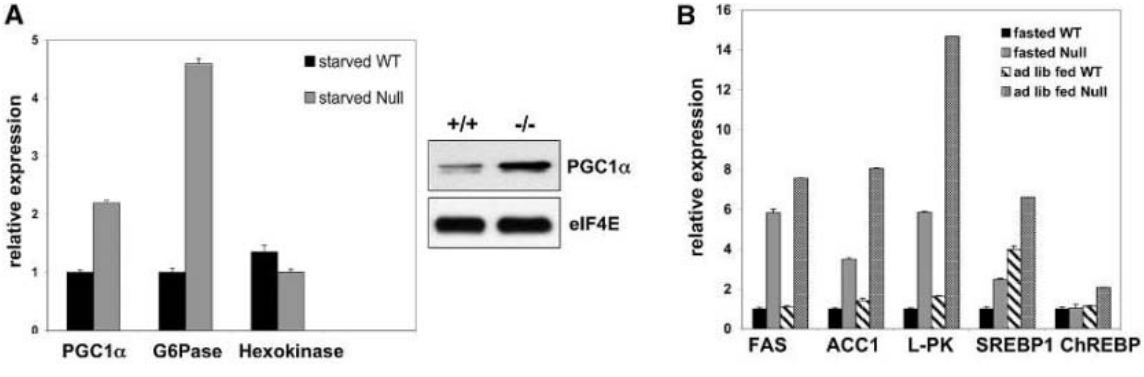

Fig. 3. Gluconeogenic and lipogenic gene expression is elevated in LKB1-deficient livers. (**A**) The left panel shows qRT-PCR examining the expression levels of mRNA for indicated gluconeogenic genes from the livers of mice of indicated genotypes and conditions 3 weeks after Cre administration. Expression was normalized to hypoxanthine-guanine phosphoribosyl transferase (HPRT) and equilibrated to the lowest-value condition for each gene. The right panel shows immunoblot analysis of PGC-1α or eIF4E (loading control) from fasted mice of indicated genotypes 6 weeks after Cre injection. (**B**) qRT-PCR for lipogenic target genes on liver samples as in (A). Mice were either fasted or fed ad lib. The induction of lipogenic targets is lower under ad lib fed conditions than for mice re-fed after fasting conditions (*49*). qRT-PCR data represent the mean + SEM for samples analyzed in triplicate.

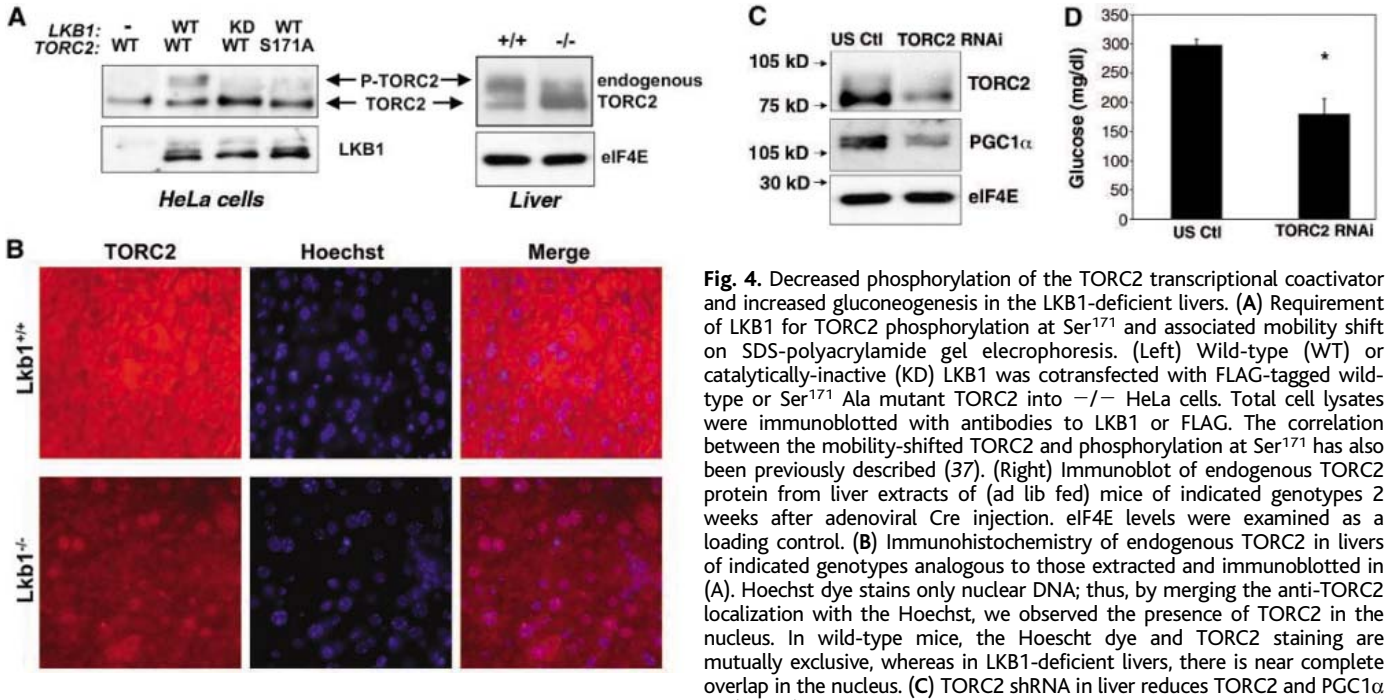

Fig. 4. Decreased phosphorylation of the TORC2 transcriptional coactivator and increased gluconeogenesis in the LKB1-deficient livers. (**A**) Requirement of LKB1 for TORC2 phosphorylation at Ser^{171} and associated mobility shift on SDS-polyacrylamide gel elecrophoresis. (Left) Wild-type (WT) or catalytically-inactive (KD) LKB1 was cotransfected with FLAG-tagged wild-type or Ser^{171} Ala mutant TORC2 into −/− HeLa cells. Total cell lysates were immunoblotted with antibodies to LKB1 or FLAG. The correlation between the mobility-shifted TORC2 and phosphorylation at Ser^{171} has also been previously described (*37*). (Right) Immunoblot of endogenous TORC2 protein from liver extracts of (ad lib fed) mice of indicated genotypes 2 weeks after adenoviral Cre injection. eIF4E levels were examined as a loading control. (**B**) Immunohistochemistry of endogenous TORC2 in livers of indicated genotypes analogous to those extracted and immunoblotted in (A). Hoechst dye stains only nuclear DNA; thus, by merging the anti-TORC2 localization with the Hoechst, we observed the presence of TORC2 in the nucleus. In wild-type mice, the Hoescht dye and TORC2 staining are mutually exclusive, whereas in LKB1-deficient livers, there is near complete overlap in the nucleus. (**C**) TORC2 shRNA in liver reduces TORC2 and PGC1α protein levels. Adenovirus encoding TORC2 shRNA or a control scrambled shRNA (US ctl) was introduced by tail-vein injection into L/L mice that had been tail-vein injected with adenoviral Cre 2 weeks earlier. Five days after adenoviral shRNA injection, mice were fasted for 18 hours. Total-cell lysates were made from the liver and immunoblotted with indicated antibodies. (**D**) Blood glucose levels in Cre-injected L/L mice reduced by TORC2 shRNA. Adenovirus shRNA was administered as above and fasting glucose levels were monitored. Data represent the mean + SEM for five mice of each group. $P < 0.01$, *t* test.

phosphorylation was increased in livers from wild-type mice injected with metformin, but not in livers deficient in LKB1 (Fig. 5A). We then examined whether metformin was capable of reducing blood glucose levels in mice in which LKB1 was deleted in the liver. To ensure that the regimen of metformin we were using was effective in comparable control mice, we placed adenovirus Cre–treated L/L mice and adenovirus Cre–treated wild-type littermates on a high-fat diet for 6 weeks. We then treated these mice, or ob/ob obese mice, with metformin for 3 days and examined blood glucose levels from fasting animals. Metformin treatment reduced blood glucose by more than 50% in the wild-type mice on a high-fat diet. Metformin treatment also lowered blood glucose in the ob/ob mice by 40%. However, there was no reduction in blood glucose in the mice in which LKB1 had been deleted in the liver.

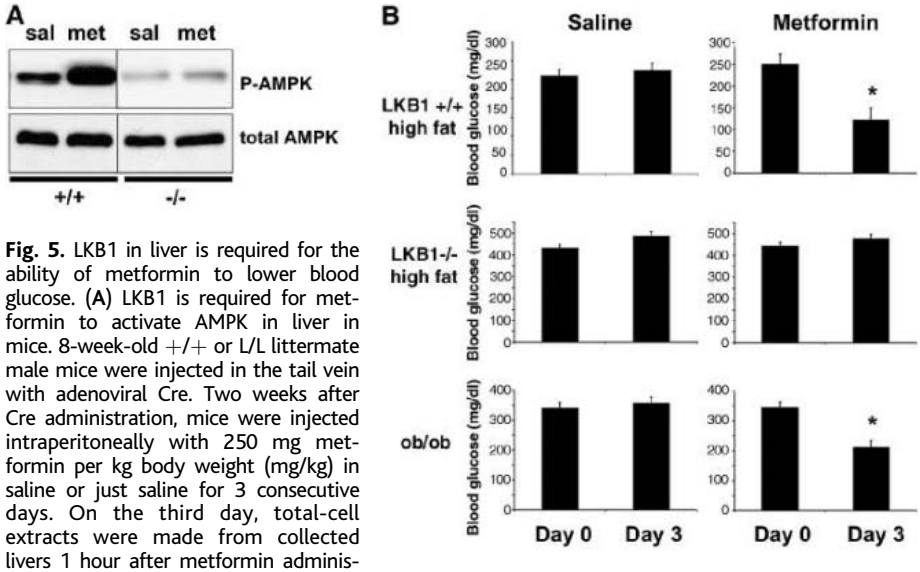

Fig. 5. LKB1 in liver is required for the ability of metformin to lower blood glucose. (**A**) LKB1 is required for metformin to activate AMPK in liver in mice. 8-week-old +/+ or L/L littermate male mice were injected in the tail vein with adenoviral Cre. Two weeks after Cre administration, mice were injected intraperitoneally with 250 mg metformin per kg body weight (mg/kg) in saline or just saline for 3 consecutive days. On the third day, total-cell extracts were made from collected livers 1 hour after metformin administration. Liver extracts were immunoblotted with antibody to phospho-Thr^{172} AMPK or total AMPK antibodies. (**B**) LKB1 in liver is required for the ability of metformin to lower blood glucose. 8-week-old +/+ or L/L littermate male mice were injected in the tail vein with adenoviral Cre and placed on a high-fat diet (55% fat, 24% carbohydrate, Harlan Teklad, Madison, WI) for 6 weeks. 8-week-old ob/ob male mice were obtained from Jackson Laboratory. Mice were fasted for 18 hours, then blood glucose was measured. Starting the next day, mice were injected intraperitoneally with 250 mg/kg metformin in saline or just saline for 3 consecutive days. On the third day, mice were fasted overnight and blood glucose was measured. Data represent the mean + SEM for five mice of each group. $*P < 0.001$, *t* test.

Conclusions. Our results provide direct evidence that the LKB1 tumor suppressor is the major upstream activating kinase for AMPK in liver. We cannot rule out minor roles for other kinases, but under all conditions we examined, the loss of LKB1 was mirrored by loss of AMPK phosphorylation. Similarly, LKB1 appears to be the major AMPKK in skeletal muscle (*45*).

We elucidate here a signal transduction pathway that governs the synthesis of glucose in the liver. The activation of an upstream kinase (LKB1) in turn regulates downstream kinases (AMPK and SIK) that phosphorylate a transcriptional coactivator (TORC2), resulting in its inactivation through sequestration in the cytoplasm. This pathway normally integrates cellular (AMPK) and hormonal (SIK) inputs to negatively regulate transcriptional events that promote synthesis of gluconeogenic enzymes. In the absence of LKB1, no kinase is active to phosphorylate TORC2, and gluconeogenesis occurs without these metabolic checkpoints. This pathway in mammalian liver is func-

tionally analogous to control of feeding on carbon sources in budding yeast. In yeast, switching growth onto nonfermentable sugars activates the AMPK homolog Snf1 through phosphorylation by upstream kinases that are homologous to LKB1. Activated Snf1 then phosphorylates the transcriptional regulator Mig1, which causes its translocation from the nucleus to the cytoplasm, altering gene expression that allows survival under the nutrient-poor environment.

Metformin has been used clinically for decades (*43*). Our data provide genetic proof that AMPK activation is absolutely required for the glucose-lowering action of metformin in intact animals. The deletion of LKB1 in the liver did not impair AMPK activation in muscle, yet it eliminated the effect of metformin on serum glucose levels. This result suggests that in mice, metformin primarily decreases blood glucose concentrations by decreasing hepatic gluconeogenesis.

LKB1 also acts as a tumor suppressor. Thus, increased CREB-dependent or SREBP-1–dependent transcription could have a role in LKB1-dependent tumorigenesis. Constitutive activation of CREB transcription contributes to oncogenesis in human salivary tumors and clear cell sarcomas (*46–48*).

These findings reinforce the emerging intimate relationship that exists between physiological control of metabolism and cancer. The mTOR, insulin, and LKB1 pathways represent a fundamental eukaryotic network governing cell growth in response to environmental nutrients. Dysregulation of each contributes to both diabetes and cancer.

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Figs. S1 to S6
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A Systems Model of Signaling Identifies a Molecular Basis Set for Cytokine-Induced Apoptosis

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Signal transduction pathways control cellular responses to stimuli, but it is unclear how molecular information is processed as a network. We constructed a systems model of 7980 intracellular signaling events that directly links measurements to 1440 response outputs associated with apoptosis. The model accurately predicted multiple time-dependent apoptotic responses induced by a combination of the death-inducing cytokine tumor necrosis factor with the prosurvival factors epidermal growth factor and insulin. By capturing the role of unsuspected autocrine circuits activated by transforming growth factor–α and interleukin-1α, the model revealed new molecular mechanisms connecting signaling to apoptosis. The model derived two groupings of intracellular signals that constitute fundamental dimensions (molecular "basis axes") within the apoptotic signaling network. Projection along these axes captures the entire measured apoptotic network, suggesting that cell survival is determined by signaling through this canonical basis set.

Despite extensive molecular-level information on how external stimuli affect cell fate, there is minimal understanding of how such intracellular processing occurs at a systemwide level. Most extracellular "inputs" initiate complex signaling patterns that propagate through an intracellular network to change the response "outputs" that determine a cell's phenotype (*1*). Molecular signaling through this network is branched (fig. S1) and dynamically interconnected to the molecular history of the previous inputs, signals, and outputs (*2*). Thus, we sought to develop a mathematical formalism to connect signals and outputs in such a way that cellular responses could be predicted from molecular signaling patterns alone.

To reduce the biological complexity of cellular signal processing, experimental systems usually monitor changes in one defined extracellular stimulus (for example, a soluble cytokine) and one output response (such as apoptosis). However, physiological input stimuli are not processed in isolation, because signaling networks constantly receive

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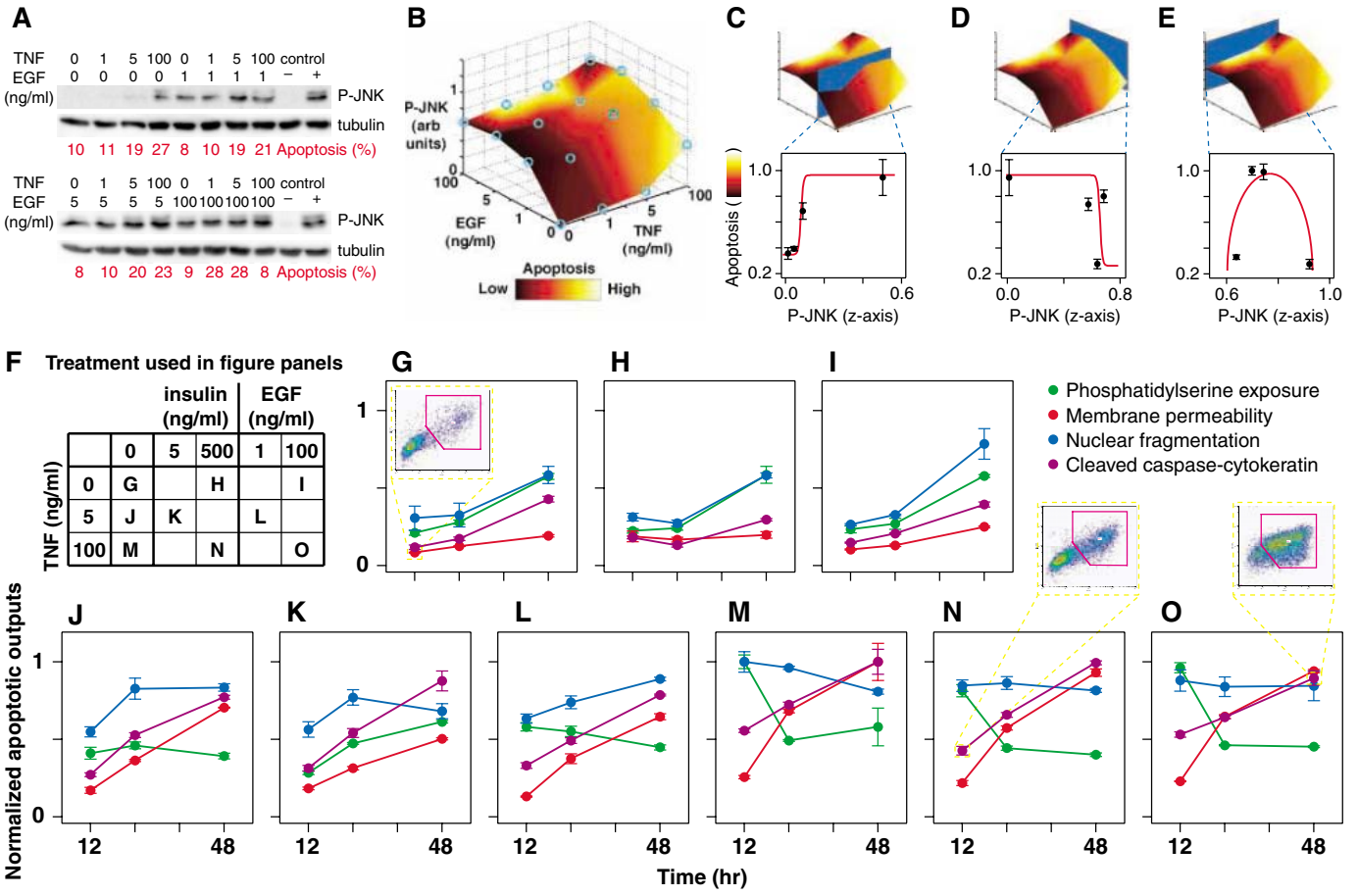

Fig. 1. JNK phosphorylation after multi-input cytokine stimulation fails to correlate with apoptotic responses. (**A**) JNK phosphorylation and apoptosis in HT-29 cells treated with TNF, EGF, or both. P-JNK was analyzed at 15 min by quantitative Western blotting with tubulin as a loading control, and apoptosis was measured at 24 hours by cleaved caspase-cytokeratin staining and flow cytometry (*9*). (**B**) Response surface for P-JNK (*z* axis) and apoptosis (color bar) induced by the input described in (A). (**C** to **E**) Lack of a correlation between JNK phosphorylation and apoptosis. P-JNK appeared to be (C) proapoptotic, (D) antiapoptotic, or (E) uninvolved in apoptosis depending on the experimental "slice" through the TNF-EGF signaling space. (**F**) Experimental design for TNF, EGF, and insulin stimulation. Letters correspond to the experimental treatment, used in the respective figure panels, for which 19 molecular signals (Table 1) (*11*) and apoptotic outputs were measured. In addition, signals and apoptotic outputs were measured in cells stimulated with 0.2-ng/ml TNF and 1-ng/ml insulin (*9*). The carrier was always 0.02% dimethyl sulfoxide (DMSO). (**G** to **O**) Apoptotic outputs by flow cytometry (*9*). In (G), (N), and (O), the insets depict representative density plots of the cleaved caspase^{+}-cleaved cytokeratin^{+} population. All flow cytometry measurements were normalized to the maximum observed apoptosis for phosphatidylserine exposure (25%), membrane permeability (67%), nuclear fragmentation (21%), and cleaved caspase-cytokeratin (77%). Data are presented as the mean ± SEM of triplicate biological samples in panels (C) to (E) and (G) to (O).

additional inputs from changing environmental conditions, such as nutrient availability, cell density, and exposure to the extracellular matrix (*3*). To investigate multi-input signal processing, large-scale "systems biology" approaches have been proposed. However, most of the analyses to date have concentrated on characterizing signals downstream of individual inputs (*4*, *5*).

Studying multiple input stimuli requires information about the network as a whole; otherwise, intracellular changes in signal transduction molecules (called "molecular signals" hereafter) can appear paradoxical. For example, c-Jun N-terminal kinase (JNK) is a protein that has been reported to be proapoptotic (*6*), antiapoptotic (*7*), or uninvolved in apoptosis (*8*) in different cell systems. To investigate this JNK-apoptosis link further, we added multiple combinations of tumor necrosis factor (TNF) and epidermal growth factor (EGF) to HT-29 human colon adenocarcinoma cells and then measured the amounts of phosphorylated JNK (P-JNK) and apoptosis (Fig. 1A) (*9*). A plot of the TNF and EGF input stimuli and corresponding P-JNK signal and apoptosis outputs established a four-dimensional signal-response "surface" (Fig. 1B). "Slices" through this surface mimicking single TNF or EGF inputs could recapitulate any of the previously reported correlations between P-JNK and apoptosis (Fig. 1, C to E) (*6*–*8*). This indicated that individual molecular signals like P-JNK cannot uniquely determine a cell's commitment to apoptosis, a complex output response. Quantitative experiments that dynamically sample many critical signals would be needed (*10*).

Dense experimental sampling of 7980 molecular signals and 1440 response outputs for cytokine-induced apoptosis. To investigate how signaling networks coordinate cellular output responses, we used an established multi-input system where HT-29 cells are stimulated with three biologically relevant cytokines: TNF, EGF, and insulin (*11*, *12*). The intracellular protein network downstream of these cytokine inputs is understood in reasonable detail (fig. S1). Within well-recognized network branches, 19 intracellular measurements of key receptor, kinase, caspase, and adaptor proteins were collected (Table 1 and fig. S1) (*11*). Using nine distinct pairwise combinations of TNF, EGF, and insulin (Fig. 1F), we sampled each molecular signal in triplicate at 13 time points between 0 and 24 hours to compile 7980 distinct molecular signals from the shared intracellular network (*11*). TNF and EGF (or insulin) are opposing cytokine inputs that promote or inhibit apoptosis, respectively (*13*, *14*), and

the intracellular measurements thus identified which molecular signals were activated en route to the cellular decision to die or to survive. However, it remained unclear how EGF- and insulin-induced molecular signals antagonized TNF-induced apoptosis.

To test whether apoptosis could be connected to the measured signaling network (*11*), we measured the cell-death phenotype for each combinatorial cytokine stimulus (Fig. 1F). The apoptotic response itself involves various cellular changes (outputs) that can be regulated independently (*15*). Individual parameters used to characterize cell death (such as loss of membrane asymmetry) only partially reflect the overall cellular response. Therefore, we selected four distinct apoptotic outputs (phosphatidylserine exposure, membrane permeability, nuclear fragmentation, and caspase substrate cleavage) and measured each output response by flow cytometry 12, 24, and 48 hours after stimulation (Fig. 1, G to O, and database S1) (*9*). Together, these output measurements constituted an apoptotic ''signature'' that characterized early (phosphatidylserine exposure), middle (caspase substrate cleavage and membrane permeability), and late (nuclear fragmentation) responses of apoptosis (the biological outputs in our system).

Apoptotic signatures were measured for the nine cytokine input combinations (Fig. 1F), revealing temporal and cytokine dose-dependent features that would have been missed by examining single apoptotic outputs alone. Membrane permeability (red) and caspase substrate cleavage (purple) measured dead cells cumulatively (*16*). Therefore, these outputs increased monotonically with time and TNF dose (Fig. 1, G, J, and M). In contrast, phosphatidylserine exposure (loss of membrane asymmetry before membrane permeability) and nuclear fragmentation (digestion of DNA before complete cellular fragmentation) were transient cell states (*16*) that could increase and decrease with time and input dose (Fig. 1, G to O).

High concentrations of EGF and insulin antagonized TNF-induced cell death in a similar manner, particularly reducing apoptotic responses at early times (Fig. 1, M to O, and fig. S2). Low concentrations of EGF and insulin elicited different output responses. EGF reduced TNF-induced membrane permeability at 48 hours but increased transient phosphatidylserine exposure at 12 hours (Fig. 1, J and L; $P < 0.05$, Student's *t* test with Bonferroni correction). In contrast, insulin reduced TNF-induced membrane permeability at 12 and 48 hours, and phosphatidylserine exposure was decreased at 12 hours but higher at 48 hours compared with TNF alone (Fig. 1, J and K; $P < 0.05$). These measured apoptotic signatures provide evidence that different apoptotic outputs can be controlled separately, depending on the input stimulus. For example, membrane permeability is most commonly associated with secondary production of reactive oxygen species (*17*), whereas phosphatidylserine exposure is thought to involve caspase- and Ca^{2+}-dependent processes (*18*). The JNK family protein kinases (Fig. 1A) have been implicated in reactive oxygen signaling (*19*, *20*) but are thought to be largely independent of Ca^{2+} signaling (*21*). Thus, relating the intracellular network dynamics to the complete apoptotic signature requires more information than can be provided by individual molecular signals, like JNK1.

Table 1. Signaling network measurements. Biological functions were assigned based on the most-recognized property of the protein. Molecular signals indicate the biochemical property of the protein that was measured. Assay indicates whether the protein was measured by high-throughput kinase activity assay (*10*), antibody microarray (*33*), or quantitative Western blotting (*12*).

Protein name	Biological function	Molecular signal	Assay
IKK	Ser kinase	Kinase activity	Kinase assay
JNK1	Ser-Thr kinase	Kinase activity	Kinase assay
MK2	Ser-Thr kinase	Kinase activity	Kinase assay
EGFR	Receptor Tyr kinase	Phosphorylation (Tyr^{1068})	Ab microarray
		Total amount	Ab microarray
		Phospho/total ratio	Ab microarray
MEK	Dual-specificity kinase	Phosphorylation (Ser^{217}/Ser^{221})	Western blot
ERK	Ser-Thr kinase	Kinase activity	Kinase assay
IRS1	Adaptor-scaffold	Phosphorylation (Ser^{636})	Western blot
		Phosphorylation (Tyr^{896})	Western blot
Akt	Ser-Thr kinase	Phosphorylation (Ser^{473})	Ab microarray
		Total amount	Ab microarray
		Kinase activity	Kinase assay
		Phosphorylation (Ser^{473})	Western blot
		Phospho/total ratio	Ab microarray
FKHR	Transcription factor	Phosphorylation (Ser^{256})	Western blot
Caspase-8	Cys protease	Zymogen amount	Western blot
		Cleaved amount	Western blot
Caspase-3	Cys protease	Zymogen amount	Western blot

A partial least-squares model predicts the 12 cytokine-induced apoptotic outputs from a 660-element signaling vector. We sought to determine whether multiple molecular signals in combination could quantitatively capture the entire apoptotic signature as a response and predict apoptosis more globally. We designed a mathematical formalism that could identify the information content within each molecular signal that most closely mapped onto the output responses. The resulting mapping of lumped signals to corresponding responses might then allow us to identify the most relevant ''information variables'' for apoptosis and use these variables to predict apoptotic responses to stimuli outside the training set.

It was unclear what aspect of a dynamically sampled molecular signal should fill the role of an information variable for apoptosis. For example, in addition to measurements of kinase activity at various time points, it was not known if other data such as the maximum activity, the rate of rise of activity, or the time when peak activity occurred also contained useful information. Therefore, we defined a panel of time-dependent signaling ''metrics'' that could be derived empirically from any dynamic signal (Fig. 2A). Each of the metrics [for example, activity of the mitogen-associated protein kinase (MAPK) extracellular signal–regulated kinase (ERK) at 5 min, ERK activity at 15 min, peak ERK activity, and the abundance of the phosphorylated (active) MAPK kinase MEK (P-MEK) at 5 min] can then be represented by an ''axis'' along which particular multi-input stimuli project (Fig. 2C).

In total, we extracted 30 to 40 metrics (table S1) from each time course of a molecular signal to form a composite ''metric set'' (Fig. 2A). Metric sets were defined for all 19 molecular signals, forming a group of individual axes that together define a 660-dimensional signaling space. The projection of a multi-input stimulus along these axes creates a ''signaling vector'' of 660 column elements corresponding to the 30 to 40 metrics from each of the 19 measured molecular signals (Fig. 2B). The apoptotic outputs were similarly concatenated to form an apoptosis vector, where the 12 column elements are the four apoptotic outputs at three time points each (Fig. 2A). Each input stimulus has its own particular signaling and apoptosis vectors, so these were calculated separately for each of the nine treatment combinations (Fig. 1F).

We sought to identify the best mapping of the 660-dimensional signaling metric space onto the 12-dimensional output response space. A simple linear mapping would require the 7920-element coefficient matrix

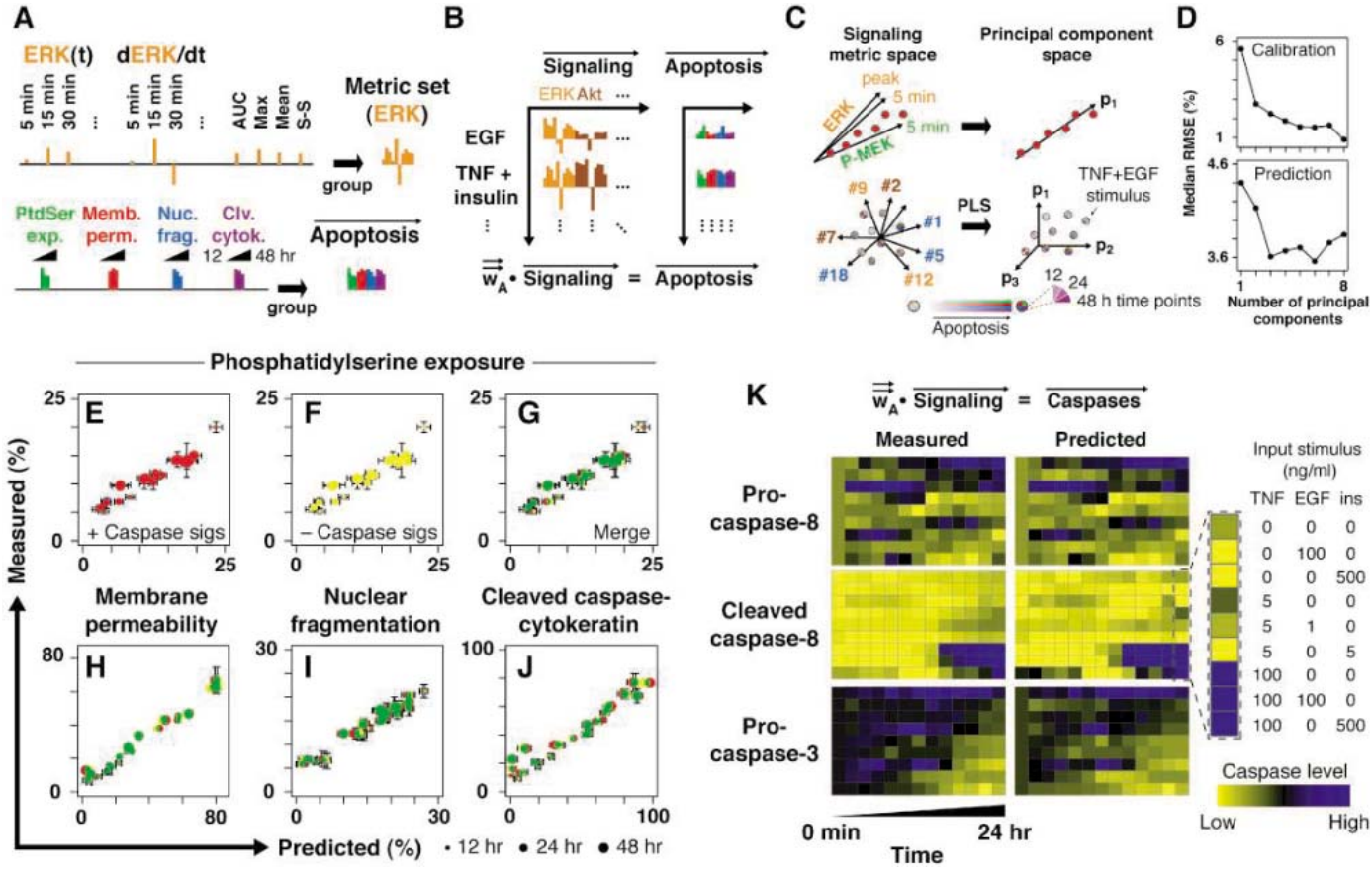

Fig. 2. A data-driven principal components-based model correctly predicts apoptosis and caspase activation from molecular signals activated by multi-input TNF, EGF, and insulin stimulation. (**A**) Extraction of signaling and response metrics. (Top) Time-course measurements (*11*) of the signaling network were used to group individual time points (*t*), instantaneous derivatives (*d*/*dt*), area under the curve (AUC), and the maximum (Max), mean, and steady-state (S-S) values and to form a signaling metric set, in this example for ERK. The activation slope and decay rates for signaling peaks were also incorporated (*9*). (Bottom) Individual apoptotic output time points were concatenated for each treatment into an apoptosis vector. (**B**) Construction of the PLS apoptosis model. Individual signaling metric sets were concatenated into a single signaling vector for each treatment condition, and these vectors then regressed against the corresponding apoptotic response vectors (*22*). w_A is the coefficient matrix of the apoptosis regression model. (**C**) PLS-based supervised decomposition of signaling vector space into principal components. (Top) A simplified example of dimensionality reduction by principal components analysis. In this example, collinear axes such as peak ERK activity, ERK activity at 5 min, and P-MEK levels at 5 min could be reduced into a single principal component axis (p_1). (Bottom) Principal component axes were captured in a supervised manner to maximize prediction of apoptotic responses. In the full PLS model, the four apoptotic outputs (red, green, blue, and purple quandrants of each data point) at three time points (12, 24, and 48 hours slices within quadrants) were oriented along three principal component axes (p_1, p_2, and p_3) determined to contain the essential signaling information for predicting apoptosis. Each point corresponds to one multi-input stimulus, such as TNF+EGF, and the shading of the point corresponds qualitatively to the extent of measured apoptosis. The numbered axes (left) indicate separate metrics extracted from different molecular signals, shown in (A). (**D**) RMSE of calibration and prediction of apoptotic outputs by the PLS model as a function of increasing number of principal components. An optimum model with three components was selected. (**E** to **G**) Correlation plots between measured phosphatidylserine exposure (*y* axis) and cross-validated predictions of phosphatidylserine exposure (*x* axis) by the PLS model including (red) and not including (yellow) caspase signals. The merged overlay is shown in green. Marker size corresponds to the response time point at 12 (•), 24 (●), and 48 (●) hours. Data are presented as the mean ± SEM, and model uncertainties were estimated by jack-knifing (*22*). (**H** to **J**) Correlation plots between measured and cross-validated predictions of membrane permeability, nuclear fragmentation, and caspase-substrate cleavage. Data are presented as in (E) to (G). (**K**) Comparisons between measured caspase levels and cross-validated predictions from a specific PLS model of caspase activation. Signaling metric vectors from noncaspase molecular signals were regressed against the 0- to 24-hour time-point measurements of procaspase-8, cleaved caspase-8, and procaspase-3. w_A is the coefficient matrix of the caspase regression model. The nine rows in the measured and predicted color coding correspond to the nine treatment combinations shown in Fig. 1F. Each region of the heat map was normalized separately for comparison.

(12 rows by 660 columns) that best transformed the signaling space into the response space (Fig. 2B), a calculation that would be impossible to solve uniquely given only nine multi-input conditions. To simplify the signal-to-response mapping and retain biological meaning, we first assumed that some of the signaling metric dimensions were either redundant or irrelevant. For instance, the peak activity of ERK contains the same information as the ERK activity at 5 min, when the ERK peak often occurred (Fig. 2C). Likewise, other axes (e.g., metrics at 0 min, before the stimulus) merely scrambled the projections because they pointed in directions unrelated to apoptosis (Fig. 2C). These redundant and uninformative axes could be deemphasized or eliminated without any loss of information about the apoptotic outputs. Second, we assumed that the remaining informative axes could be compressed by linear combination into a small number of dimensions that retained the critical apoptotic information and thus constituted a biologically relevant basis set for the signal-to-response mapping. For instance, proteins like MEK and ERK are part of the same signaling pathway and were thus activated similarly. Although not identical, the information in many MEK and

ERK metrics pointed in collinear directions that could be combined into a MEK-ERK "super axis" that retained the projection with fewer dimensions (Fig. 2C).

To reduce unnecessary axes and condense important axes mathematically, we used partial least-squares (PLS) regression, which simplifies dimensions on the basis of their covariance with a specified dependent variable (*22*, *23*). The original 660-dimensional signaling space was reduced to a series of super axes that together best orient the measured apoptotic-output elements within the apoptosis vector (Fig. 2, A and C). PLS modeling, like singular value decomposition (*24*), calculates super axes as an orthogonal set of "principal components," which contain linear combinations of the original 660 metric dimensions weighted by their contribution to the apoptotic outputs (Fig. 2C). Principal components are calculated iteratively so that successive PLS dimensions are regressed against the apoptotic-output information not captured by the preceding component. After several iterations, including more dimensions becomes undesirable, because the residual information is so small that new principal components capture spurious fluctuations in the outputs, such as measurement error and noise, rather than meaningful data (*22*).

To optimize the number of model dimensions, we examined the root-mean-squared error (RMSE) between the measured apoptosis vector and the values from models with increasing numbers of principal components. All of the input treatments were included in the initial model training to assess the RMSE of data fitting (calibration). Each treatment was then individually withheld from the training set to construct a cross-validation model, in which an RMSE of prediction could be assessed by predicting the withheld sample. The calibrated RMSE decreased monotonically, but the predicted RMSE was minimized with just three principal components (Fig. 2D). Using the resulting three-component apoptosis model, we examined the correlation between the measured apoptotic outputs and the cross-validated predictions for each treatment (*22*). If the correct signaling information was retained by the principal components in the model, then the apoptotic outputs for TNF, EGF, and insulin stimuli not included during the model training should also be predicted. Indeed, we found a high correlation for all 12 apoptotic outputs, with predictions that were accurate to within 94% of the measured values overall (Fig. 2, E to J). Although the 12 individual apoptotic outputs differed quantitatively from one another (Fig. 1, G to O), their stimulus-dependent changes were almost entirely captured by a single PLS model of the intracellular network (Fig. 2, E to J). The 660 dimensions of the original signaling space (Fig. 2C) had thus been condensed to three dimensions, which were enriched in the molecular signals most useful for predicting the apoptotic outputs. Furthermore, specifying the dynamic state of the intracellular signaling network was absolutely essential—an equivalent PLS model given only cytokine-input concentrations (Fig. 1F) rather than intracellular signaling metrics could not correctly predict the apoptotic outputs (45% accuracy) (*25*).

The original measurements (*11*) of the signaling network contained several direct effectors of apoptosis, such as caspases (Table 1) (*26*). The model would obviously be less valuable if these late-effector signals were providing all of the predictive power to the model. To test whether caspase metrics were required for accurate predictions, we removed all of the caspase signals from the model and rederived the principal component axes. The resulting predictions were essentially identical (Fig. 2, E to J). Thus, non-caspase signals in the network contained more than enough information to predict the apoptotic outputs quantitatively. Furthermore, molecular signals activated before the initial onset of apoptosis were themselves sufficient for predicting the apoptotic signature. We found that a separate PLS apoptosis model derived exclusively from signaling measurements made at 0 to 4 hours after cytokine addition was accurate to within 81% (fig. S3).

To examine the relationship between other molecular signals and late effector caspases directly, we next removed the apoptotic outputs altogether and defined the procaspase-8, cleaved caspase-8, and procaspase-3 time-point measurements as a new set of cellular outputs (Fig. 2K). Using the remaining network measurements, the PLS model predicted the caspase response dynamics within 81% accuracy (Fig. 2K). Together, these results suggested that both the caspase effector signals and the final cellular output responses were encoded by the upstream signaling network.

Model-driven discovery of apoptosis regulation by means of autocrine circuits. In HT-29 cells, two regulated autocrine stimuli—transforming growth factor–α (TGF-α) and interleukin-1α (IL-1α)—cooperate with TNF to activate molecular signals in the network (Fig. 3A) (*11*). Whether these autocrine circuits contribute substantially to TNF-induced apoptosis is not known. We therefore used the PLS model to predict what the apoptotic signature would be when autocrine TGF-α and IL-1α circuits were disrupted with either an antibody to the EGF receptor (C225) or an IL-1 receptor antagonist (IL-1ra), and the cells were then treated with TNF. All 19 molecular signals were measured from 0 to 24 hours (*11*) and provided as input data to the PLS model. We then measured the actual TNF+C225- and TNF+IL-1ra–induced apoptotic signatures experimentally (*9*) and compared these with the model predictions. This experiment was a particularly stringent test of the model, because neither TGF-α nor IL-1α had been part of the original training set (Fig. 1F).

We observed a 90% correlation between the measured apoptotic outputs and the model predictions when the two autocrine loops were disrupted individually (Fig. 3B), indicating that the model could predict the contributions of cytokines other than TNF, EGF, and insulin. Furthermore, upstream molecular signals alone were highly predictive of downstream effector caspase activation after TNF+C225 and TNF+IL-1ra stimuli (prediction within 91% of measured values; Fig. 3C). Therefore, the contributions of autocrine TGF-α and IL-1α to TNF-induced apoptosis had been implicitly and correctly incorporated throughout models of apoptotic outputs as well as caspase activation.

Disruption of the IL-1α autocrine loop decreased most apoptotic outputs in cells responding to TNF (Fig. 3D), suggesting that autocrine IL-1α was an extracellular positive-feedback circuit for TNF-induced apoptosis. In contrast, disruption of TGF-α signaling by C225 led to large changes in TNF-induced activation of the network but did not lead to any clear overall changes in apoptosis (Fig. 3D). Some outputs, such as phosphatidylserine exposure, were increased in cells treated with C225 ($P < 10^{-5}$, two-way analysis of variance). Others, such as caspase substrate cleavage, were decreased ($P < 0.05$), whereas 6 of the 12 individual apoptotic outputs did not change in a statistically significant manner (*9*, *25*).

TGF-α is a member of the EGF family (*27*), and treatment of cells with EGF was shown to reduce apoptosis (Fig. 1, M and O). Why then did blocking autocrine TGF-α with C225 not increase apoptosis overall? First, in HT-29 cells, autocrine TGF-α activates a prodeath signal by inducing late (12- to 24-hour) release of autocrine IL-1α (Fig. 3A and fig. S4) (*11*). Second, we reasoned that the late, prodeath IL-1α signal must be offset by some unknown late, prosurvival signal. Concurrent prodeath and prosurvival signals at late times could then neutralize one another and explain the net lack of an effect of autocrine TGF-α on apoptosis. To help identify this late, prosurvival signal, we examined the coefficients within the PLS model that quantified the contribution of each signal to apoptosis (Fig. 2B), because the model correctly predicted the mixed apoptotic response resulting from autocrine TGF-α perturbation (Fig. 3B). Early MAPK-activated protein kinase 2 (MK2) kinase activity in the model correlates with

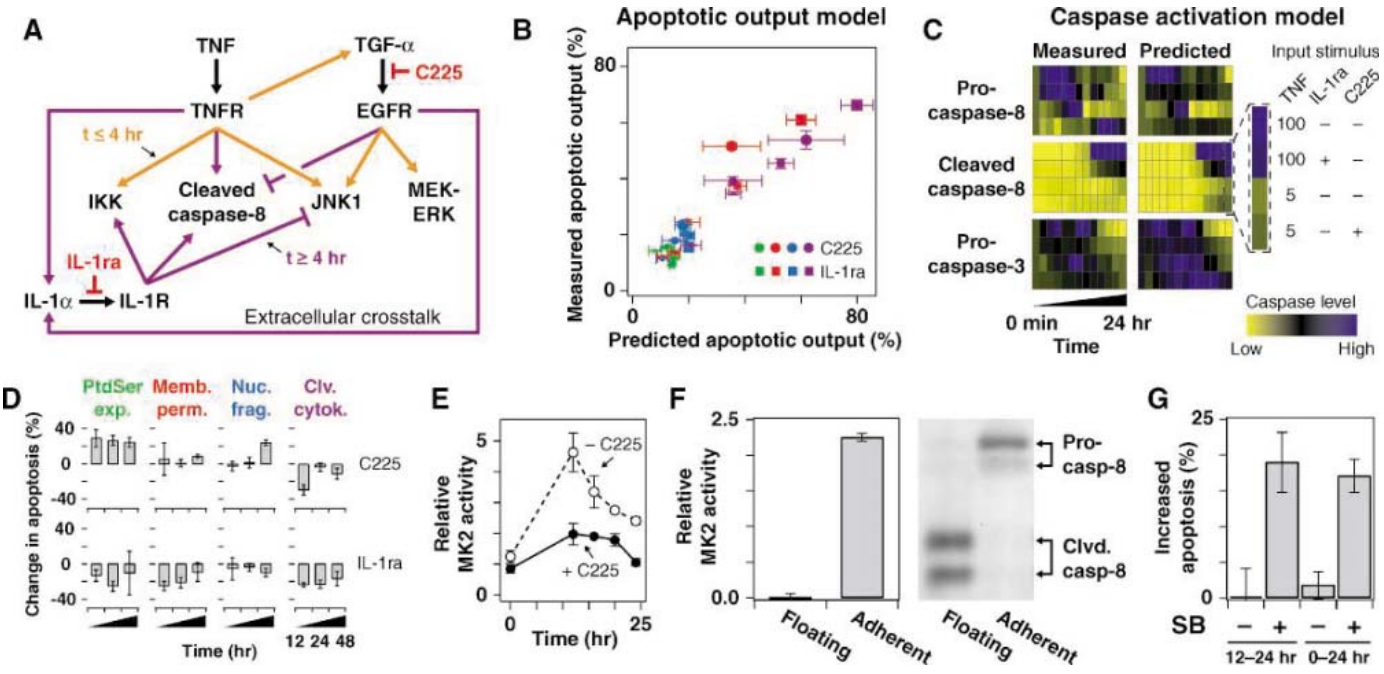

Fig. 3. The principal components-based model captures hidden autocrine feedback in the signaling network and identifies late MK2 activity as a TGF-α–induced prosurvival signal. (**A**) Diagram of TNF-induced autocrine circuits in HT-29 cells (*11*). Orange arrows indicate fast pathways (before 4 hours) and purple arrows indicate slow pathways (after 4 hours). C225 and IL-1ra were used as pharmacological inhibitors of autocrine TGF-α and IL-1α, respectively. (**B**) The model correctly predicts TNF-induced apoptosis when the autocrine feedback circuits are disrupted by C225 and IL-1ra. Apoptotic outputs were measured as in Fig. 1, G to O, for cells treated with 5-ng/ml TNF and 10-μg/ml C225 (circle) and 100-ng/ml TNF plus 10-μg/ml IL-1ra (square). Marker color corresponds to the apoptotic index (as in Fig. 1, G to O) and size corresponds to the time point (as in Fig. 2, E to J). Horizontal error bars indicate model uncertainty by jack-knifing (*22*). (**C**) The model correctly predicts caspase cleavage in response to TNF stimulation when the autocrine feedback circuits are disrupted. Comparisons between measured caspase levels and model predictions for the autocrine circuit perturbations. Each panel was normalized separately, and the unperturbed caspase dynamics were included for comparison. (**D**) The TNF→IL-1α autocrine circuit is proapoptotic, whereas the TNF→TGF-α circuit sends both pro- and antiapoptotic signals. Comparison of TNF-induced apoptotic outputs with and without autocrine IL-1α and autocrine TGF-α. Data are shown as percent change in apoptosis in C225- and IL-1ra–treated cells compared with unperturbed TNF-stimulated cells (*10*). (**E**) TNF-induced late MK2 activity is TGF-α dependent. Cells were stimulated with 5-ng/ml TNF in the presence or absence of 10-μg/ml C225 to block autocrine TGF-α, and MK2 activity was measured by in vitro kinase assay (*10*). (**F**) Late MK2 activity is restricted to surviving cells. (Left) Cells were treated with TNF for 20 hours, separated into floating and adherent subpopulations, and MK2 activity was assayed as in (E). Data were normalized to basal MK2 activity as described (*12*). (Right) Floating and adherent cells correspond to apoptotic and viable cells, respectively, as indicated by caspase-8 cleavage and 4′,6′-diamidino-2-phenylindole (DAPI) staining (*25*). (**G**) Late MK2 activity is a prosurvival signal. Cells were treated for 24 hours with 100 ng/ml TNF in the presence or absence of the inhibitor SB202190 (SB) during the indicated times and assayed for apoptosis by the presence of caspase substrate cleavage. For (B) and (D) to (G), data are presented as the mean ± SEM of triplicate biological experiments (*11*).

apoptosis (*25*); by contrast, the model revealed that MK2 signaling at times after 12 hours was strongly anticorrelated with apoptosis, implicating MK2 as a prosurvival kinase at later times. In agreement with this, when autocrine TGF-α was blocked by C225, MK2 activity at late times was inhibited (Fig. 3E) (*11*, *25*). Thus, both the model and experiment suggested that late MK2 activity was a prosurvival signal activated by autocrine TGF-α.

If effectively prosurvival, then MK2 activity at late times should be present primarily in viable cells. MK2 signaling was therefore analyzed separately in live and apoptotic cells by measuring the floating and adherent subpopulations of TNF-treated cells. All MK2 activity was detectable only in the adherent (viable) cells (Fig. 3F). If we permitted the early phase of MK2 activity to occur in response to TNF but rapidly inhibited the late phase with SB202190, a small-molecule inhibitor of the MK2-activating kinase p38 (*28*, *29*), we observed a significant increase in cell death at 24 hours (Fig. 3G; $P < 10^{-5}$, Students t test). Taken together, these experiments demonstrate that the signal-to-response linkages implicated by the PLS model can reveal new biological mechanisms that would not be easily recognized without a mathematical formalism.

Redundant encoding of signaling components and critical roles of MAPKs in PLS predictions of apoptosis. In the full model, 660 metrics derived from 7980 signaling measurements were used to predict apoptosis (Fig. 2, E to J, and Fig. 3B). In retrospect, it was not clear whether apoptotic outputs could be predicted equally well by a reduced number of metrics derived from smaller, more tractable experiments. We found that a model containing only the 20 most informative metrics, as determined by the relative magnitude of their coefficients in the model (table S2) (*9*), was nearly as predictive of apoptosis as one that used all 660 metrics (Fig. 4A). A noteworthy feature of the top 20 metrics was that they were not the obvious metrics we would have chosen on the basis of our basic understanding of the regulation of apoptosis. Activation slopes of Akt and insulin receptor substrate 1 (IRS1) phosphorylation and integrated peaks of JNK1 and inhibitor of nuclear factor κB kinase (IKK) signaling were included, but caspase metrics were missing entirely (table S2). Use of fewer than these top 20 metrics, in isolation, gave substantially less effective predictions (*25*), supporting our original hypothesis that individual signaling measurements would not broadly predict cell responses (Fig. 1, C to E).

High predictive ability of the top 20 metrics (Fig. 4A) suggested redundancy in the signaling information contained within the original 660-metric model. To investigate this, we sequentially removed various portions of the most informative metrics and then recalculated the prediction of apoptosis by

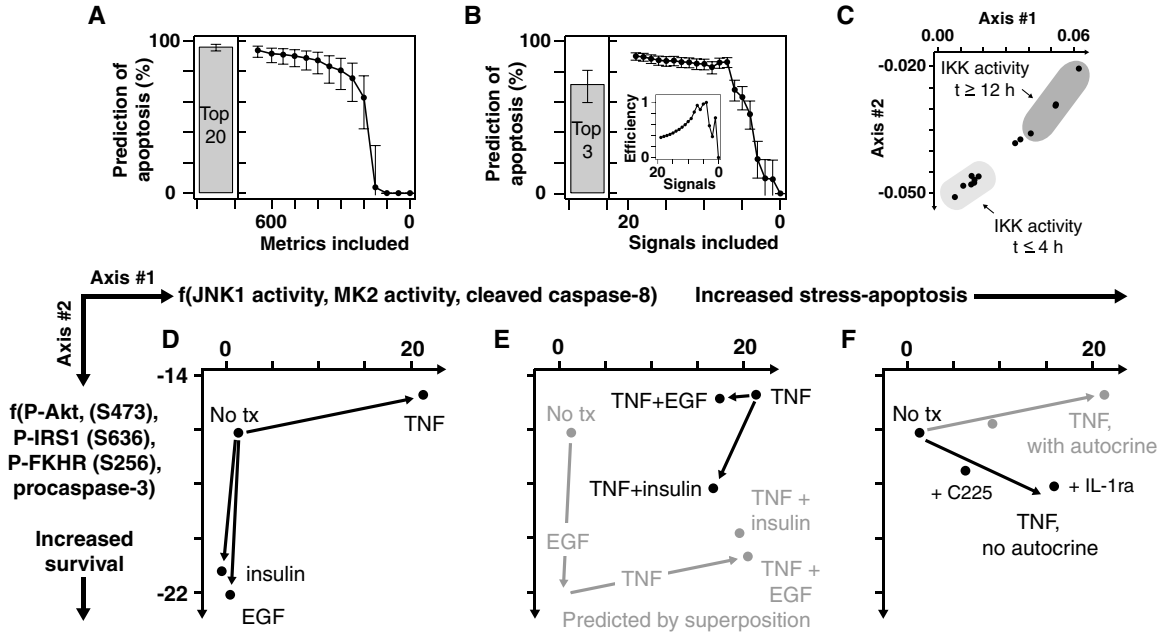

Fig. 4. Two orthogonal stress and survival axes link complex stimuli to apoptosis. (**A** and **B**) The principal component–based model is redundantly encoded. (A) Decreased accuracy of prediction of apoptotic responses to TNF, EGF, and insulin with a decreasing number of signaling metrics. (B) Decrease in accuracy of prediction of apoptotic responses to autocrine signals with a decreasing number of molecular signals. Both metrics and molecular signals were eliminated sequentially from best to worst on the basis of their variable importance in the principal-component projection (*9*). (Inset) Predictive efficiency as a function of number of molecular signals included. To calculate efficiency, the TNF-EGF-insulin apoptotic predictions in (B) were divided by the number of molecular signals in the submodel. For (A) and (B), data are presented as the central prediction ± 90% Fisher Z-transformed confidence intervals. (**C**) The two principal components can correspond to distinct time-resolved mechanisms of molecular-signal activation. Contribution of IKK activity time-point metrics to axes 1 and 2. Early and late IKK time points are shaded in light and dark gray, respectively. A reciprocal time-dependent change in projection along axes 1 and 2 was observed for MK2 (*25*). (**D** to **F**) The intracellular signaling network is defined by two orthogonal stress and survival axes that link complex stimuli to apoptosis. (D) Cytokine inputs project along orthogonal stress and survival axes (axes 1 and 2) of the PLS model. (E) Cytokine combinations project differently from linear superposition of isolated cytokine stimuli. EGF in combination with TNF directly antagonizes stress pathway signaling, whereas insulin in combination with TNF both antagonizes stress signaling and induces separate prosurvival signaling pathways. The linear superposition of single-input TNF, EGF, and insulin projections from Fig. 4E is shown in gray. (F) Autocrine feedback circuits rotate the TNF-induced signaling network to reinforce stress responses and suppress any signaling down the survival axis. For (D) to (F), samples were projected using the model scores as described (*22*).

cross-validation. Up to the top 350 metrics could be eliminated from the full list of 660 metrics before the apoptosis model lost all predictive ability (Fig. 4A). This implied that the full set of 660 biological metrics was redundantly encoded with the stimulus-specific information required to mediate all of the apoptotic outputs (*30*, *31*). We also analyzed the contributions of individual proteins (that is, the 19 molecular signals) based on the average information contained in their derived metrics. The top three molecular signals—JNK1, MK2, and ERK—belonged to MAPK cascades (*25*). A model given only metrics from these three signals performed nearly as well as the full PLS model in predicting the effects of autocrine perturbations (Fig. 4B). A model derived from the seven least informative molecular signals was also predictive (Fig. 4B). Together, these findings suggest that measurements of three to seven relevant intracellular molecular signals are sufficient to predict network-dependent output responses. Prediction efficiency (defined as the relative predictive ability divided by the number of molecular signals included in the model) was maximal with four to five molecular signals (Fig. 4B, inset).

The PLS model identifies stress-apoptosis and survival signaling axes. We examined the relationship between all of the signaling network measurements and the input treatments as signals propagated through the model's first two principal components (*22*), which predicted the apoptotic outputs within 92%. These components are the two main lumped contributions of the signaling metrics, which form a pair of orthogonal axes defining the optimal two-dimensional slice through the signaling data set (*22*). We found that certain signals and treatments were clearly overrepresented in these dimensions. The first principal component, axis 1, was oriented toward stress and apoptotic pathways and included early JNK1 activity, early MK2 activity, and late cleaved caspase-8 metrics (table S3). In contrast, the second principal component, axis 2, appeared to constitute a global survival signal that included phosphorylated Akt (P-Akt), phosphorylated IRS1 (P-IRS1), phosphorylated Forkhead transcription factor (P-FKHR), and procaspase-3 metrics (table S4). The specific molecular signals emphasized in these components were entirely consistent with the known molecular mechanisms that link these signaling proteins to apoptosis (fig. S1).

Using the principal component axes, we could reanalyze the signaling contributions to apoptosis from cells exposed to single or combined cytokines. Certain signals, such as IKK, contributed differently to the stress-apoptosis and survival axes depending upon the time point when the molecular signal was measured. Early IKK activity induced directly by the TNF receptor (TNFR) was weighted predominantly along prosurvival axis 2 (Fig. 4C). However, IKK activity after 12 hours, which occurs indirectly in response to an autocrine signal from IL-1α (Fig. 3A) (*11*), contributed more to the stress-apoptosis axis (Fig. 4C). Thus, the PLS model had revealed that the same molecule, such as IKK, can convey either pro- or antiapoptotic messages, depending on the timing and mechanism of activation.

For individual cytokines, we found that TNF treatment alone projected strongly along prodeath axis 1, whereas isolated EGF and insulin treatments mapped exclusively on prosurvival axis 2 (Fig. 4D). This reinforced our original intuition that TNF and EGF-insulin stimuli act upon orthogonal and antagonistic signaling axes for apoptosis. In contrast, the multi-input projections were markedly different from what would be predicted by a summation of the single-input treatments (Fig. 4E, gray). TNF, EGF, and insulin each lost a fraction of their original projections along the two axes, indicating that the input stimuli were

antagonized when added in combination (Fig. 4E). The TNF+EGF and TNF+insulin treatments were distinctly separated from one another: EGF appeared to antagonize TNF-induced apoptosis by specifically reducing the projection along the stress-apoptosis axis 1 without any change along axis 2 (Fig. 4E); in contrast, insulin actively promoted prosurvival signaling along axis 2 while also inhibiting stress-apoptosis signaling along axis 1. Therefore, analyzing the multi-input stimuli through these model-derived biological "basis axes" (Fig. 4D) helped to reveal the different network strategies used by EGF and insulin to antagonize TNF-induced apoptosis.

Finally, to determine the contributions of TNF-induced autocrine circuits in the model, we mapped the TNF+C225 and TNF+IL-1ra treatments (Fig. 4F). The projection of TNF along the stress-apoptosis axis (Fig. 4F) was enforced by the autocrine circuits, which increased the contribution along axis 1 and decreased the contribution along axis 2. This is consistent with the notion that regulated autocrine circuits provide microenvironment-dependent feedback to cells during phenotypic decision processes, such as death-survival (*11*, *32*). Furthermore, it illustrated directly that effects of complex environmental stimuli were entirely contained within the two canonical basis axes distilled from the original 660-dimensional signaling metric space by the PLS model (Fig. 4D).

In summary, by using a systems approach that combines quantitative experiments with data-driven modeling, we identified two canonical axes—a stress-apoptosis axis and a survival axis—that together constitute a molecular basis set for the signaling network that controls apoptosis. These axes capture the dynamic intracellular signal processing of diverse stimuli, including autocrine-feedback circuits. Our work illustrates how a complex signaling network can be reduced empirically to a much simpler computational model that is directly tied to biological mechanism.

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Supporting Online Material

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Materials and Methods
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REPORTS

Mach-Zehnder Interferometry in a Strongly Driven Superconducting Qubit

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We demonstrate Mach-Zehnder–type interferometry in a superconducting flux qubit. The qubit is a tunable artificial atom, the ground and excited states of which exhibit an avoided crossing. Strongly driving the qubit with harmonic excitation sweeps it through the avoided crossing two times per period. Because the induced Landau-Zener transitions act as coherent beamsplitters, the accumulated phase between transitions, which varies with microwave amplitude, results in quantum interference fringes for $n = 1$ to 20 photon transitions. The generalization of optical Mach-Zehnder interferometry, performed in qubit phase space, provides an alternative means to manipulate and characterize the qubit in the strongly driven regime.

The development of artificial atoms with lithographically defined superconducting circuits presents a new paradigm of quantum solid-state physics (*1*), allowing the realization and exploration of new macroscopic quantum phenomena (*2*–*9*), and also holding promise for applications in quantum computing (*10*). Of the various effects demonstrated with qubits, the most important are time-dependent coherent phenomena. Those include the observation of Rabi oscillations in charge, flux, and phase qubits (*2*, *5*–*9*), entanglement of two qubits (*11*), coherent oscillation (*12*) and bifurcation (*13*) in multilevel systems, and the demonstration of basic elements of coherent control (*14*–*16*). Artificial atoms strongly coupled to photons have opened the arena of "circuit quantum electrodynamics" (c-QED) (*17*, *18*).

Here, we demonstrate an application of superconducting qubits to quantum physics, realized in a strongly driven flux qubit and described in terms of a Mach-Zehnder (MZ) interferometer. The conventional MZ setup

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uses two beamsplitters: The first divides an optical signal into two coherent waves that travel along paths with different effective lengths, and the second recombines and superposes these waves, leading to quantum interference fringes in the measured output signal. In a driven qubit, according to an idea discussed by Shytov *et al.* (*19*), the beamsplitters can be realized by Landau-Zener (LZ) transitions at a level avoided crossing. Over one oscillation period of the driving field, the qubit is swept through the avoided crossing twice (Fig. 1A). Starting from the marker, at the first LZ transition (time t_1), the ground state $|0\rangle$ is split into a coherent superposition of the ground and excited states, $|1\rangle$ and $|0\rangle$, which, after evolving independently and accumulating a relative phase $\Delta\theta_{12}$, interfere at the second LZ transition (time t_2). The corresponding qubit-state energy evolution (first period, Fig. 1B) between the recurrent LZ transitions (shaded region) provides a phase-space analog to the two arms and the beamsplitters of an optical MZ interferometer (top left, Fig. 1B). The interference phase

$$\Delta\theta_{12} = \frac{1}{\hbar}\int_{t_1}^{t_2}\varepsilon(t)dt,\ \varepsilon(t) = \varepsilon_{|0\rangle}(t) - \varepsilon_{|1\rangle}(t) \quad (1)$$

where $\hbar = h/2\pi$, h is the Planck constant, and ε is the energy difference between states $|0\rangle$ and $|1\rangle$, depends on the magnitude of the qubit energy detuning excursion for times $t_1 < t < t_2$. The interference fringes in the occupation probability correspond to integer and half-integer values of $\Delta\theta_{12}/2\pi$. Known as Stückelberg oscillations with Rydberg atoms (*20*, *21*), this mechanism can be applied to quantum control (*22*).

The qubit MZ interferometer differs in a number of ways from an optical interferometer. First, instead of a photon, the interferometry is performed with the use of the quantum state of a qubit. Second, in the qubit, we have the interference of paths in phase space rather than in coordinate space; the phase $\Delta\theta_{12}$ (Eq. 1) is determined by the qubit level splitting, which plays the role of the optical path length. Finally, because they are more fragile than photons and easier to decohere, qubit states can be manipulated in a coherent fashion only at relatively short time scales.

We used a periodic driving signal, a harmonic variation of the qubit detuning $\varepsilon(t)$

$$\mathcal{H} = -\frac{1}{2}(\Delta\sigma^x + \varepsilon(t)\sigma^z),$$
$$\varepsilon(t) = \varepsilon_0 + A_{\mathrm{rf}}\cos\omega t \quad (2)$$

where Δ is the tunnel splitting, σ^x and σ^z are Pauli matrices, ε_0 is the detuning proportional to dc flux bias, and A_{rf} is the radio frequency (rf) field amplitude proportional to the rf flux bias (*23*). In this case (Fig. 1B), we have cascaded LZ transitions which occur when the driving amplitude exceeds detuning, giving rise to the interference fringes at $A_{\mathrm{rf}} > |\varepsilon_0|$ (Fig. 1C). Although the phase $\Delta\theta_{12}$ equals the shaded area in Fig. 1B and is dependent on A_{rf}, the total phase gained over one period, $\theta = [1/\hbar]\int\varepsilon(t)dt = 2\pi\varepsilon_0/\hbar\omega$, equals the difference of the shaded and unshaded areas and is independent of A_{rf}. As consecutive pairs of LZ transitions (consecutive MZ interferometers) interfere constructively when $\theta = 2\pi n$, the fringes will appear around the resonance detuning values

$$\varepsilon_{0,n} = nh\nu \quad (3)$$

where $n = 0, 1, 2, \ldots$ and $\nu = \omega/2\pi$. Another interpretation of this condition is that the sequential LZ transitions excite multiphoton resonances.

Although coherent multiphoton resonances between discrete states of an rf-driven charge qubit have been reported (*5*, *24*) and multiphoton transitions used to drive Rabi oscillations in a flux qubit (*25*, *26*), in these works as well as in the earlier work on quantum dot systems (*27*, *28*), only a few photon transitions could be observed, with coherence quickly weakening as rf amplitude increased (*29*). In contrast, we were able to observe coherent resonances of very high order, up to $n = 20$, which requires driving the system at a high rf amplitude. The fringes for high n are as clear as those for $n \cong 1$, indicating that the qubit preserves a substantial amount of coherence even in the strongly driven regime.

We realized a tunable artificial atom with a niobium persistent-current qubit (Fig. 2A), a superconducting loop interrupted by three Josephson junctions (*30*). When the qubit loop is threaded with a magnetic flux $f_q \approx \Phi_0/2$, the system exhibits a double-well potential-energy landscape (fig. S1). The classical states of the wells are persistent currents I_q with opposing circulation, described by energy bands $\pm\varepsilon_0/2 = \pm I_q\Phi_0\delta f_q$ linear in the flux detuning $\delta f_q \equiv f_q - \Phi_0/2$. The double-well barrier allows quantum tunneling of strength Δ, opening the avoided

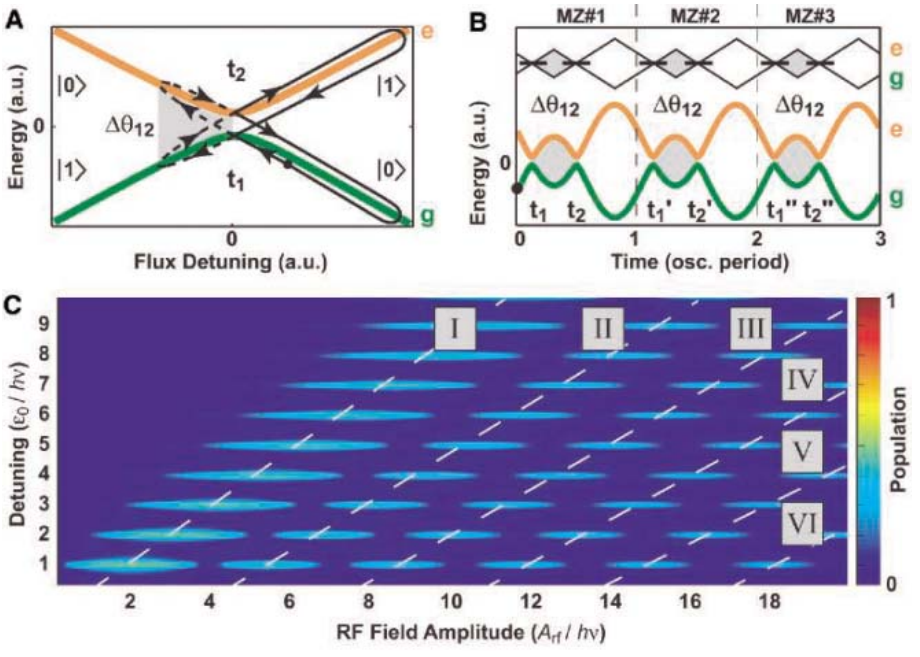

Fig. 1. MZ interference in a strongly driven qubit. (**A**) Starting at the dot marker, the qubit state is swept by an rf field. After an LZ transition at the first avoided crossing (time t_1), the resulting superposition state of $|0\rangle$ and $|1\rangle$ (dashed lines) accumulates a phase $\Delta\theta_{12}$ (shaded region) and interferes at the return LZ transition (time t_2). The qubit state is subsequently driven away from the avoided crossing and then returns to the starting flux position. This single period of qubit evolution is a single MZ interferometer. Depending on the interference phase $\Delta\theta_{12}$, amplitude may build in the excited state. a.u., arbitrary units. (**B**) The corresponding qubit energy variation induced by a periodic rf field, Eq. 2, results in an equivalent optical cascade of MZ interferometers (MZ#1 to #3, top) with resonance condition Eq. 3. (**C**) The population of the qubit excited state, Eq. 6, as a function of rf amplitude A_{rf} and detuning ε_0. Note the interference fringes (I to VI) at $A_{\mathrm{rf}} > \varepsilon_0$ and the multiphoton resonances at $\varepsilon_0 = nh\nu$.

crossing near $\delta f_q = 0$ (Fig. 1A). Detuning the flux tilts the double well and, thereby, modifies its eigenenergies and eigenstates. The qubit states are read out with a dc superconducting quantum interference device (DC-SQUID), a sensitive magnetometer that distinguishes the flux generated by the circulating currents. The device was fabricated at MIT Lincoln Laboratory (*23*).

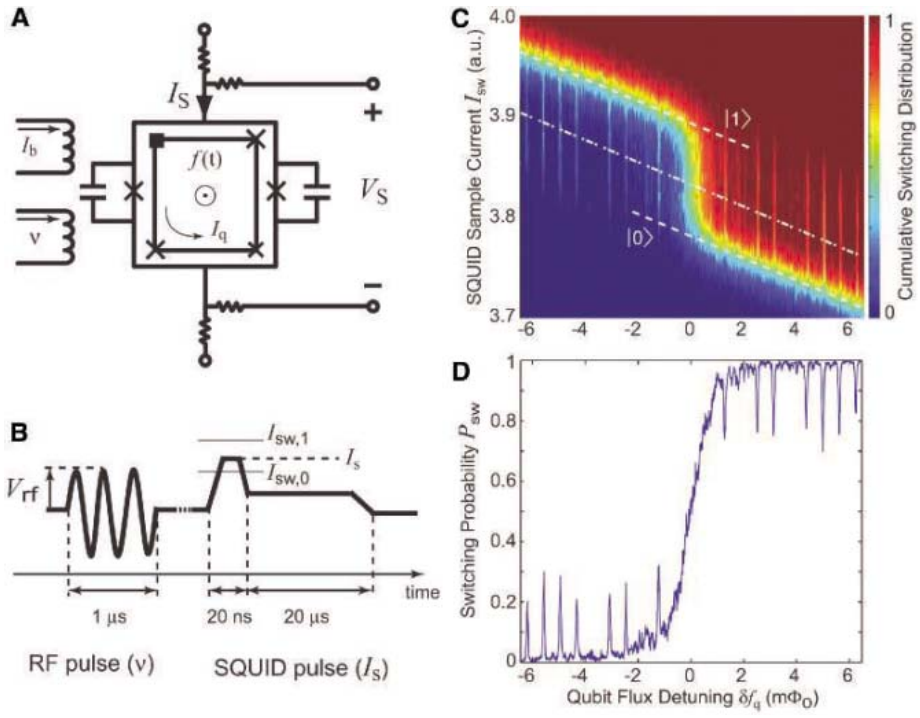

Fig. 2. Multiple resonances in a strongly driven flux qubit. (**A**) Circuit schematic of the three-junction flux qubit (inner loop) with circulating current I_q and the DC SQUID readout (outer loop); Josephson junctions are indicated with an ×. A time-dependent flux $f(t) \propto \varepsilon(t)$ threading the qubit is a sum of the flux bias due to the dc current I_b and a pulsed ac current at frequency ν irradiating the qubit and driving transitions between its quantum states. The SQUID is shunted by two 1-pF capacitors to lower its resonance frequency. Resistors mark the environmental impedance isolating the SQUID. (**B**) The time sequence for the rf pulse (duration 1 μs and rf-source voltage V_{rf}) and SQUID sample current I_s. A repetition period of 5 ms allows for equilibration between trials. (**C**) A cumulative switching-probability distribution of the qubit as a function of I_s and the qubit flux detuning δf_q under rf excitation at $V_{rf} \approx 0.12$ V_{rms} and ν = 1.2 GHz. Multiphoton transitions are observed between the qubit states |0⟩ and |1⟩ and are symmetric about the qubit step ($\delta f_q = 0$ mΦ$_0$). a.u., arbitrary units. (**D**) The 1D switching probability P_{sw} extracted from (C) (dash-dotted line scan).

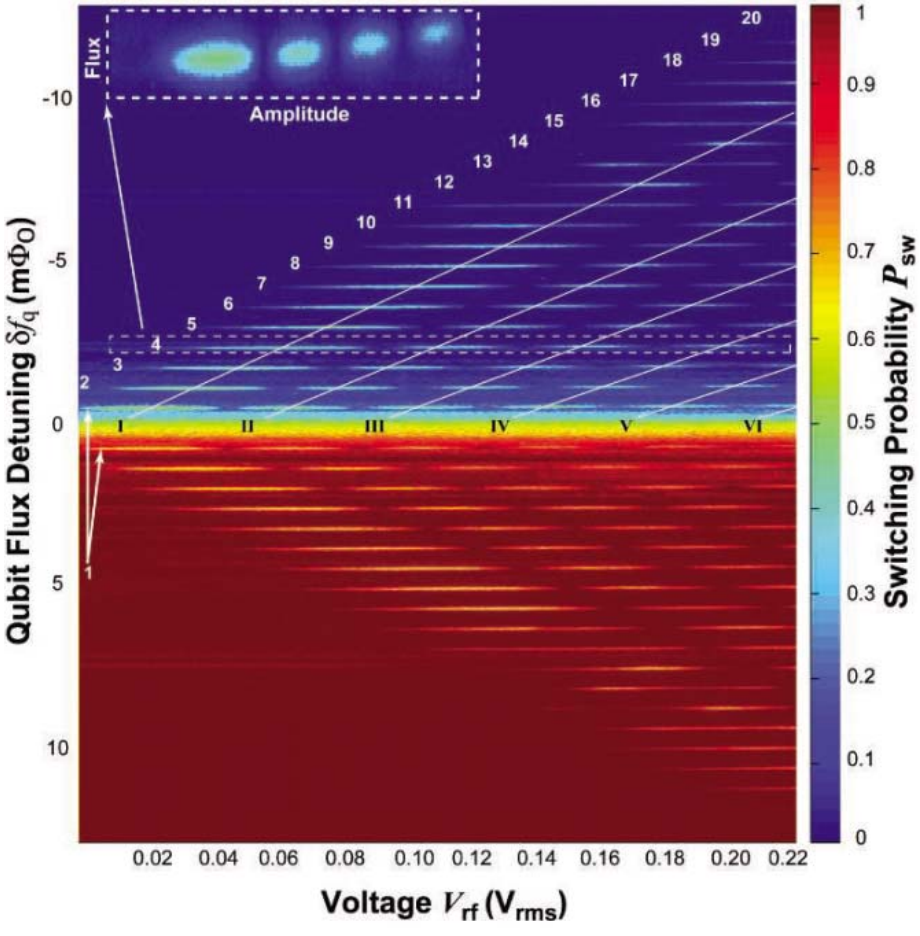

Fig. 3. Multiphoton interference fringes show a Bessel staircase. Switching probability P_{sw} is plotted as a function of qubit flux detuning δf_q and voltage V_{rf} at frequency ν = 1.2 GHz. *n*-photon resonances are labeled 1 to 20. Each *n*-photon resonance exhibits oscillations in P_{sw} resulting from a MZ-type quantum interference that results in a Bessel dependence $J_n(\lambda)$, where λ is the rf amplitude scaled by *h*ν (Eq. 4). Roman numerals mark the interference fringes of $J_n(\lambda)$ (solid white lines). The *n*-photon resonances are symmetric about the qubit step (0 mΦ$_0$). (Inset) Close-up of the $n = 4$ photon resonance.

We drove transitions between the qubit states by applying a 1-μs rf pulse (Fig. 2B) at frequency ν and rf-source voltage V_{rf} (*31*). After a short (≈10-ns) delay, we read out the qubit state by driving the DC-SQUID with a 20-ns "sample" current I_s followed by a 20-μs "hold" current. The SQUID will switch to its normal state voltage V_s if $I_s > I_{sw,0}$ ($I_s > I_{sw,1}$), corresponding to qubit states $|0\rangle$ and $|1\rangle$. By sweeping the sample current and flux detuning while monitoring the presence of a SQUID voltage over many trials, a cumulative switching-distribution function was generated, revealing the "qubit step" (Fig. 2C). At specific values of flux detuning, the rf field at ν = 1.2 GHz becomes resonant with the energy level separation, allowing *n*-photon absorption, Eq. 3; this results in a partial population transfer between the qubits states, manifest as regularly spaced "spikes" in Fig. 2C. We obtained one-dimensional (1D) scans of the "switching probability" P_{sw} (the population of state $|0\rangle$) shown in Fig. 2D by following a flux-dependent sample current $I_{sw,0} < I_s < I_{sw,1}$ (dash-dotted line in Fig. 2C). Such 1D scans were then accumulated as a function of the rf source parameters V_{rf} (Fig. 3) and ν (fig. S2).

The switching probability P_{sw} (color scale in Fig. 3) versus qubit flux detuning δf_q and voltage V_{rf} at frequency ν = 1.2 GHz is shown in Fig. 3 (*23*). The *n*-photon resonances, labeled by *n* = 1 to 20, exhibit MZ interference fringes (I to VI) as a function of V_{rf}. The fringes exhibit a Bessel-function dependence, $J_n(\lambda)$, so we call the steplike pattern in Fig. 3 a "Bessel staircase." For each of the *n*-photon resonances, we took a higher resolution scan (e.g., Fig. 3 inset) and fitted the resonance areas and widths in Fig. 4 (*23*).

Multiphoton transitions at the resonances (Eq. 3) in the strong driving regime, $|A_{rf}|, h\nu \gg \Delta$, occur by means of fast LZ transitions. The notion of quasi-stationary qubit levels $\pm[1/2](\varepsilon_0^2+\Delta^2)^{1/2}$ is inadequate in this regime and, instead, we use a different approach, transforming the Hamiltonian (Eq. 2) to a nonuniformly rotating frame, $\mathcal{H}' = e^{-(i/2)\phi(t)\sigma^z}\mathcal{H}'e^{(i/2)\phi(t)\sigma^z}$, where $\phi(t) = \lambda\sin\omega t$ with dimensionless rf-field amplitude

$$\lambda = A_{rf}/h\nu \qquad (4)$$

The rf field disappears from the detuning term, reappearing as a phase factor of the off-diagonal term: $\mathcal{H}' = -[1/2](\varepsilon_0\sigma^z + \Delta e^{-i\phi(t)}\sigma^+ + \text{h.c.})$, where h.c. is hermitian conjugate. Given that $\Delta \ll h\nu$, near the *n*th resonance $nh\nu \cong \varepsilon_0$ we can replace the phase factor $e^{-i\phi(t)}$ by its *n*th Fourier har-

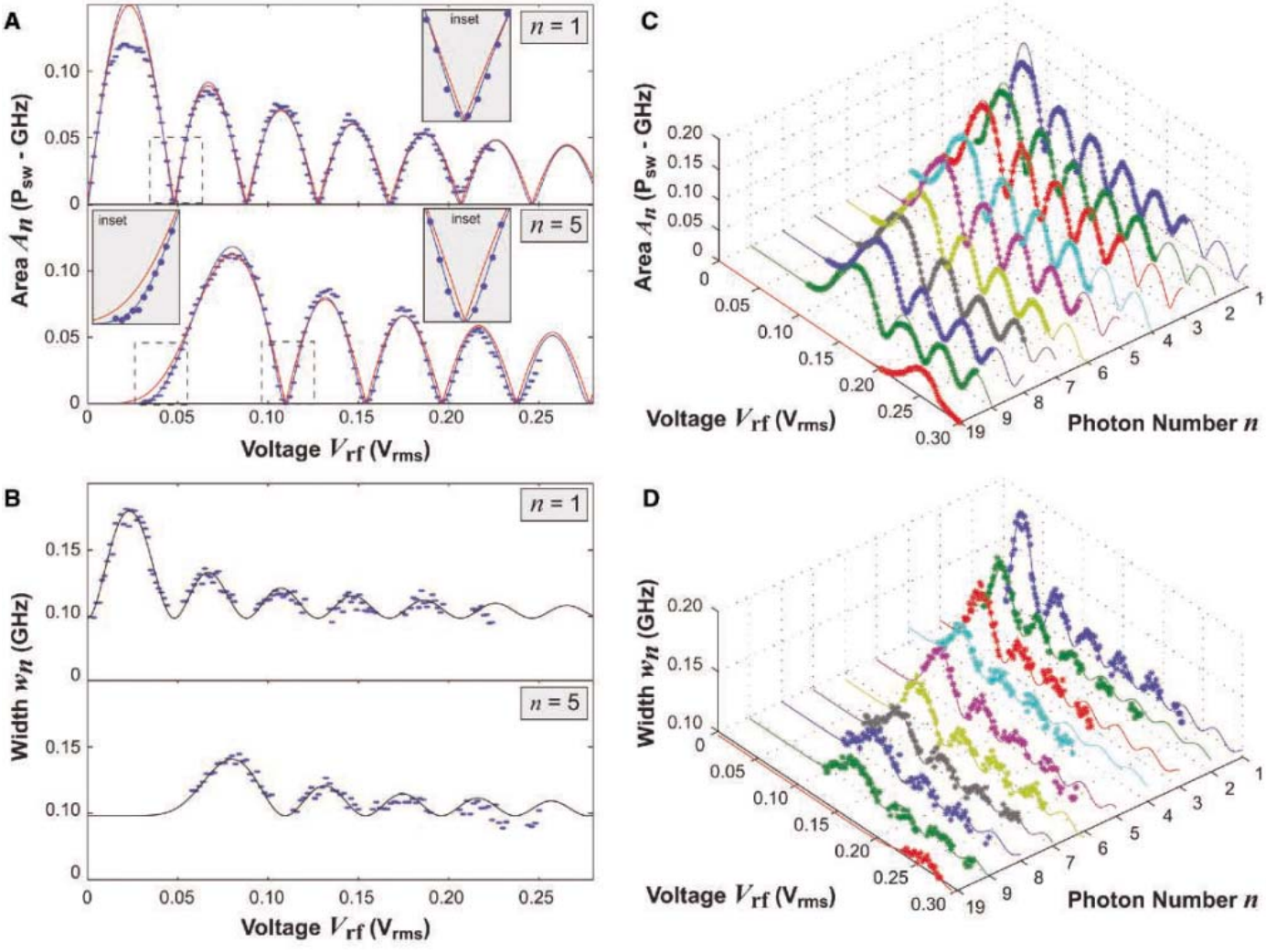

Fig. 4. Analysis of the resonance area and width. (**A**) Resonance area A_n versus voltage V_{rf} for the *n* = 1 and *n* = 5 photon transitions. The Bessel dependence $J_n(\lambda)$ is observed over several lobes. The data are best fit by functions that include decoherence (blue line) rather than omit it (red line). (Insets) Decoherence becomes more pronounced as photon number increases. (**B**) The resonance width w_n versus voltage V_{rf} for *n* = 1 and *n* = 5 also exhibits a Bessel dependence. (**C** and **D**) The area (C) and the width (D) plotted for resonances *n* = 1 to 9 and *n* = 19.

monic, $J_n(\lambda)e^{-in\omega t}$, where J_n is the Bessel function. The resulting effective Hamiltonian $\mathcal{H}' \approx \mathcal{H}_n$ is of a "rotating-field" form

$$\mathcal{H}_n = -\frac{1}{2}\begin{pmatrix} \varepsilon_0 & e^{-in\omega t}\Delta_n \\ e^{in\omega t}\Delta_n^* & -\varepsilon_0 \end{pmatrix} \quad (5)$$

where $\Delta_n = \Delta J_n(\lambda)$. The resonance approximation (Eq. 5) describes transitions at an arbitrary ratio $A_{rf}/h\nu$. Standard Rabi dynamics analysis of the Hamiltonian (Eq. 5) with the initial state $|0\rangle$ gives the time-averaged occupation probability of the excited state $P_{sw}^{(n)} = [1/2]\,|\Delta_n|^2/((\varepsilon_0 - nh\nu)^2 + |\Delta_n|^2)$. This expression predicts Lorentz-shaped resonances of width $\delta\varepsilon = |\Delta_n|$. The result, a sum of independent contributions with different n,

$$P_{SW} = \frac{1}{2}\sum_n \frac{|\Delta_n|^2}{(\varepsilon_0 - nh\nu)^2 + |\Delta_n|^2} \quad (6)$$

is displayed in Fig. 1C. The agreement with the observed resonances is notable: The oscillations in rf power, described by $J_n(\lambda)$, accurately predict both the overall profile of the fringes (Fig. 3) and the fine details, such as positions of the nodes (Fig. 4).

In the frequency dependence of P_{sw} for voltages V_{rf} = 71 mV_{rms} and V_{rf} = 7.1 mV_{rms} (fig. S2), the resonances approach the qubit step as frequency decreases, in accordance with the linear energy versus flux-detuning dependence. MZ interference fringes are again visible. The number of resonances increases at low frequencies, due primarily to the frequency dependence of λ and in lesser part, a frequency-dependent mutual coupling.

Our analysis of peak profile accounts for the relaxation and dephasing, as well as for the inhomogeneous broadening due to low-frequency noise. These effects can be separated from one another by considering the peak areas A_n, which, in contrast with the widths of the resonances w_n, are not affected by inhomogeneous broadening. The standard Bloch approach yields

$$A_n = \frac{T_1\Delta_n^2}{4\sqrt{T_1T_2\Delta_n^2 + 1}},$$
$$w_n = \frac{1}{\pi T_2^*} + \frac{\sqrt{T_1T_2\Delta_n^2 + 1}}{\pi T_2} \quad (7)$$

where $T_{1,2}$ represents the longitudinal and transverse relaxation times, and T_2^* describes the inhomogeneous broadening. These are aggregate relaxation times averaged over the periodic qubit detuning, which, in the operating limit $\varepsilon_0 \gg \Delta$, tends to overestimate T_1 and underestimate T_2 compared with their values at the avoided crossing.

Figure 4A shows the Bessel dependence of the n = 1 and n = 5 resonance areas fit by Eq. 7 including (blue) and omitting (red) times $T_{1,2}$. The corresponding resonance widths and their fittings are shown in Fig. 4B. Figure 4, C and D, show the resonance area and width, respectively, for 10 resonances, including n = 19. Fitting the areas and widths yields self-consistent estimates: $T_1 \approx 20$ μs, $T_2 \approx 15$ to 25 ns, $T_2^* \approx 5$ to 10 ns, and $\Delta/\hbar \approx (2\pi)4$ MHz. The T_1, T_2, and Δ estimates are similar to those reported by Yu *et al*. (*26*). The nearly linear behavior at the nodes of J_n (Fig. 4A) indicates that the decoherence is small compared with the splitting: $T_1T_2(\Delta/\hbar)^2 \approx 250$ for n = 1 and decreases slightly for n = 5. The fit/data discrepancy for the first fringe for n = 1, which disappears as n increases, is traced to ~20% thermal population of the excited state because of its proximity to the qubit step (supporting online material text).

This MZ interferometry technique can be applied to qubit characterization and model validation, two increasingly important research areas in quantum information science. In addition to coherence times, which can be obtained by multiple means, MZ interferometry allows the direct calibration of the microwave amplitude driving the qubit through the Bessel argument λ; we found the rf mutual coupling (±SD) to be $M_q = 100 \pm 2$ fH over all 20 resonances. The agreement between the two-level Hamiltonian in Eq. 2 and the observed resonances n = 1 to 10 in Fig. 3 is notable. The MZ technique also reveals shortcomings of the two-level model at strong driving. For example, the influence of a second MZ interferometer at the avoided crossing between the first and second excited states results in the moiré-like pattern observed for resonances n > 12. Also notable is an observed (~0.1 GHz) shift in the resonance positions at strong driving [Fig. 3 inset]. Both effects require the presence of higher excited states modeled by the full qubit Hamiltonian (*26*, *30*). The high stability and coherence of the strongly driven qubit, even at n = 20 photon transitions, illustrates not only the potential for nonadiabatic control methods (*22*), but also indicates the high potential of niobium devices fabricated in a fully planarized, scalable process for superconductive quantum computation.

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31. V_{rf} is the rf voltage at the source generator. The rf-field amplitude A_{rf}, which drives the qubit, is parameterized in units of energy, and it is proportional to V_{rf}. The proportionality constant can be inferred from the interference fringe spacing and the Bessel argument λ.

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Evidence for Macromolecular Protein Rings in the Absence of Bulk Water

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We have examined the architecture of a protein complex in the absence of bulk water. By determining collision cross sections of assemblies of the *trp* RNA binding protein, TRAP, we established that the 11-membered ring topology of the complex can be maintained within a mass spectrometer. We also found that the binding of tryptophan enhances the stability of the ring structure and that addition of a specific RNA molecule increases the size of the complex and prevents structural collapse. These results provide definitive evidence that protein quaternary structure can be maintained in the absence of bulk water and highlight the potential of ion mobility separation for defining shapes of heterogeneous macromolecular assemblies.

A substantial amount of evidence suggests that native protein structure remains largely intact upon the removal of bulk solvent (*1*). Specifically, the observation that dehydrated crystal structures of small globular proteins retain a high degree of structural homology to their fully hydrated counterparts highlights the intrinsic stability of the native fold in the absence of solvent (*2*, *3*). Multiprotein complexes have the added complexity of side chains that interdigitate across subunit interfaces to form complicated interaction networks. To date, relatively little is known of the effect of water depletion on these interactions. The noncovalent contact area between protein subunits is thought to be a major stabilizing influence (*4*), although solvent-related forces may also contribute to the stability of protein interfaces (*5*). The advent of electrospray ionization (*6*) has enabled generation of protein ions that are essentially depleted of water. Subsequent analyses using either hydrogen-deuterium exchange (*7*), optical spectroscopy (*8*), or ion mobility spectrometry (*9*–*12*), although generally limited to peptides and single proteins, have provided evidence that highly charged gas-phase ions populate a greater number of conformations compared with their solution-phase analogs (*7*). In contrast, lower charged ions retain compact conformations that resemble more closely the native fold (*10*, *11*). The conformations of multiprotein complexes in the gas phase, however, have not been addressed, primarily because the conditions and instrumentation developed to preserve such interactions are not readily coupled with established approaches that probe higher-order structure. Consequently, although it has been widely recognized that protein complexes can survive within the solvent-depleted environment of the mass spectrometer (*13*–*18*), their overall topology is unknown.

In order to investigate the architecture of water-depleted protein complexes, we selected the *trp* RNA binding attenuation protein (TRAP). This small protein (circa 8 kD) forms oligomers with 11 subunits, and x-ray analysis has demonstrated a ring topology for the complex (*19*). Previous mass spectrometry experiments showed that we can examine the stoichiometry of the complex under a variety of conditions and also enabled us to suggest a tryptophan binding mechanism (*20*). Given the large number of subunits and their ring arrangement, we reasoned that such a system would allow us to distinguish changes in collision cross section that would occur if the native ring structure of the complex were to collapse as solvent is depleted. By using high-transmission ion mobility measurements of the noncovalent protein assembly, we investigated the collision cross sections of various TRAP complexes generated by nanoflow electrospray from an aqueous solution buffered at pH = 7.0. Ion mobility separation was carried out by using a traveling wave ion guide cell within a modified quadrupole time-of-flight mass spectrometer (Materials and Methods) (*21*). This instrumental arrangement (fig. S1) allows separation of ions on the basis of their ability to traverse an environment of neutral gas molecules under the influence of a weak electric field. The time taken for an ion to travel a defined distance is recorded, and this transit time is then converted to a collision cross section, a parameter directly related to the size and overall topology of an ion (*22*). Various computational approaches are used to generate possible model structures on the basis of this information (*9*, *23*).

A mass spectrum recorded for an aqueous solution of apo TRAP shows four broad peaks corresponding to the 19+ to 22+ charge states of the 11-mer protein complex (Fig. 1A). The broadness of peaks arises from the encapsulation of solvent or buffer molecules within the assembly and is consistent with the measured mass being higher than that anticipated for naked protein subunits. For each of the charge states, the time taken to transit the ion mobility device (on the order of 15 to 30 ms) is normalized for the influence of charge and converted to a collision cross section (Fig. 1A, a to d) (Materials and Methods). The 19+ charge state has the largest collision cross section (6600 Å^2), and this measurement is in agreement with cross-section estimates derived from the ring structure determined by x-ray crystallography (*19*). The 20+ charge state exhibits a bimodal distribution, indicative of structural heterogeneity, whereas the peaks assigned to the 21+ and 22+ are the most compact, consistent with closely packed configurations of protein subunits. Overall, the collision cross sections that we have measured for apo TRAP are in accord with the native architecture and close-packed collapsed states but also encompass a range of conformers with intermediate and lower collision cross sections than those anticipated by models constructed from simple, noncompressible spheres.

To generate model structures that more accurately describe both the intermediate and highly compact structures described above, we used molecular dynamics methods. We generated a model that uses compressible spheres of the approximate diameter of TRAP subunits and a simple potential energy surface to drive the ring structure to collapse over the course of the simulation. The conformational space around this pathway is then explored with use of a random vector (*R*) that increases in magnitude in successive simulations of the same pathway (Materials and Methods). One set of simulations, including 5000 separate quaternary arrangements of TRAP, shows that the range of collision cross sections measured for the 19+ charge state encompasses the native ring architecture and includes partial ring structures as well as buckled rings (Fig. 2). In addition, the simulation was able to generate a small number of highly compact structures that agree closely with the collision cross sections measured for the most compact charge state (22+) of the apo TRAP protein complex. These compact quaternary structures are characterized primarily by protein subunits that overlap with respect to the original boundaries of the subunits defined at the outset of the simulation.

The stability of the native quaternary structure of TRAP is known to increase upon binding tryptophan (*19*). Mass spectrum and ion mobility data recorded for ions electrosprayed

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from a solution of TRAP with a two-fold excess of Trp are similar to those observed for apo TRAP (Fig. 1B). The maximum collision cross section measured for the tryptophan-bound holo form is closely similar to the apo form, consistent with tryptophan binding between protein subunits, as established crystallographically (*19*). However, significant differences can be observed by comparing the ion mobility data for the 20+ charge state of the apo and holo complexes (Fig. 1, Ad and Bc); the former displays a bimodal distribution of transit times assigned to a range of conformers, whereas for the latter a single distribution is observed, consistent with the native-like ring configuration. We therefore conclude that the putative ring-type structure of the holo form of TRAP is more stable than the apo form in the absence of bulk solvent.

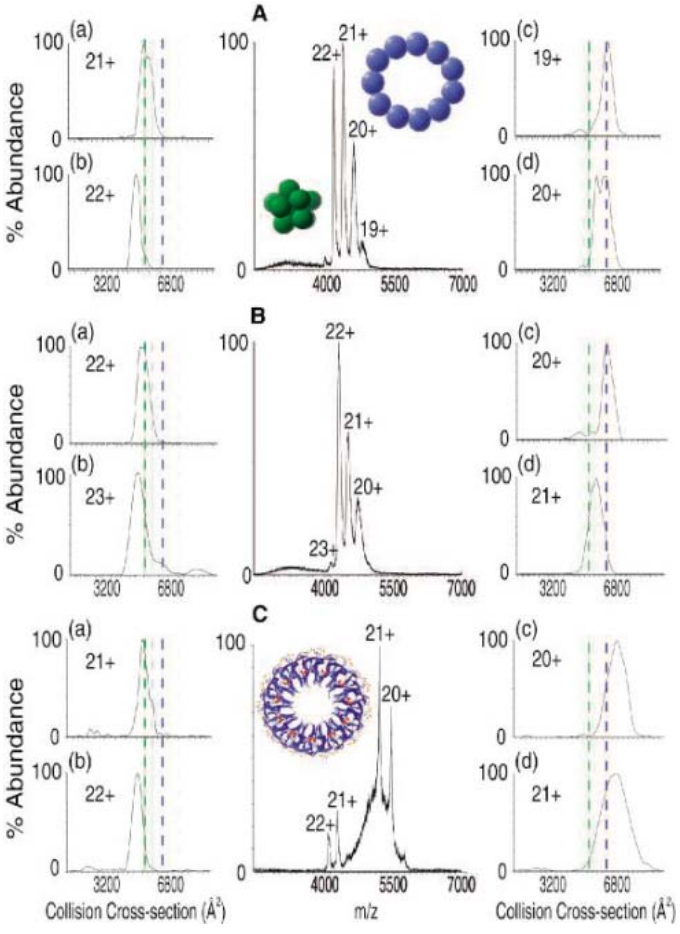

Fig. 1. Ion mobility–mass spectrometry data for the TRAP complex in ligand-bound and unbound forms. For all data, blue and green dashed lines correspond to collision cross sections for ring and collapsed structures based on the native state (6500 Å²) and close-packed icosahedral (5600 Å²) arrangements of spheres, respectively. A representation of the crystal structure of TRAP [(*19*), PDB identification number 1C9S, created using the program SIB Swiss PDB Viewer software] illustrates the positions within the complex of RNA, tryptophan (space-filling representation), and protein subunits (blue). (**A**) Mass spectrum of the intact apo TRAP complex. (a to d) Ion mobility data for charge states of the intact 11-mer TRAP complex superimposed on a collision cross-section axis. (**B**) Mass spectrum of the 11-member TRAP complex bound to 11 tryptophan molecules. (a to d) Ion mobility data for the charge states of the tryptophan-bound TRAP complex. (**C**) Mass spectrum of the intact apo TRAP complex as well as the 11-member complex bound to both 11 tryptophan molecules and a 53-base segment of RNA. Ion mobility data for 22+/21+ charge states of apo TRAP (a and b) and 20+/21+ charge states of RNA/Trp/TRAP complex (c and d).

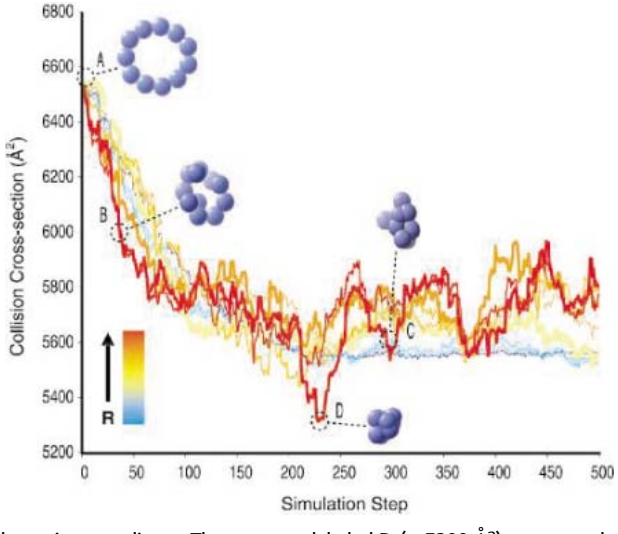

Fig. 2. Plot of collision cross section versus simulation step for 10 separate molecular dynamics simulations of the collapse of an 11-member protein complex, differing with respect to the amount of random energy given to the subunits that comprise the complex at each step in the simulation (represented by the value of *R*, the magnitude of which is indicated by the color scale shown in the lower left-hand corner of the plot). Structures A to D were selected from the simulation that correspond to the experimentally determined collision cross sections (A, ~6500 Å²; B, ~6000 Å²; and C, ~5600 Å²). Dashed circles indicate the position of the model structures on the simulated reaction coordinate. The structure labeled D (~5300 Å²) corresponds to the most compact structure generated by the simulations.

It has also been established that, in the presence of tryptophan, a 53-base segment of the *trp* leader mRNA binds around the perimeter of the TRAP complex and stabilizes the resulting assembly in solution (*20*). The mass spectrum recorded for the TRAP-Trp RNA solution shows low intensity peaks (22+ and 21+) for TRAP 11-mer, and at higher *m/z* (mass/charge) values the spectrum shows more intense peaks of the same charge states for the RNA-bound complex (Fig. 1C). For the apo TRAP ions, collision cross sections are similar to those measured for TRAP in the absence of RNA, confirming the reproducibility of our measurements (Fig. 1C, a and b). The RNA-bound species, however, have the broadest distribution of all collision cross sections (by a factor of 2), most likely arising from inherent chemical heterogeneity (Fig. 1C, c and d) (*24*). Moreover, the longest ion mobility transit times (~28 ms) of all the structures examined here are recorded for the RNA-bound species, consistent with the largest collision cross section (7400 Å²). This represents a 12% increase in collision cross section with respect to the ring structure of the apo form and is consistent with calculated values for the protein complex upon RNA binding. Our data are therefore in accord with established models that show RNA binding to the periphery of the protein complex. We also find that the contribution from collapsed structures to the distribution of conformers is negligible, in agreement with the enhanced rigidity of the ring when RNA is bound to the perimeter.

The observation that the structure of the apo and holo TRAP protein complexes change as a function of charge state is an unexpected one. We anticipated that the collision cross sections of the complex would be relatively insensitive to changes in charge state because the charge per subunit for all the ions is well below the threshold for Coulombic unfolding observed for monomeric proteins (*25*, *26*), although previous ion mobility experiments have indicated that the gas-phase structures of small proteins can vary dramatically within a narrow distribution of charge states (*10*, *11*, *26*, *27*). One explanation for the apparent collapse of protein quaternary structure at higher charge states is that minor fluctuations, caused by Coulombic repulsion, could lead to small, local aberrations in structure that subsequently collapse the native-like

ring. A second possibility is that, rather than strictly a charge-state dependence, the increased number of solvent and buffer molecules (~10 to 50) present, particularly in lower charge states, within large protein-protein complexes could contribute to their stability (*27*). A third possibility is that complexes with higher charge states (21+ or 22+) will be subject to more energetic collisions with neutral gas molecules and will consequently accumulate larger amounts of internal energy, leading to changes in structure.

To investigate the sensitivity of the various conformers to changes in internal energy, we examined collision cross sections of the apo TRAP complex as a function of activation energy by manipulating their acceleration in the atmospheric pressure interface of the instrument (Fig. 3). For the 22+ ions at the lowest activation energies (50 and 125 V), collision cross sections are indicative of close-packed collapsed structures. At 175 V the collision cross section increases, implying that the higher internal energy leads to a larger structure, consistent with the activation of ions initially in very compact configurations. The distribution of collision cross sections for 21+ ions of apo-TRAP is essentially constant throughout the change in acceleration voltage, consistent with a collapsed structure that is less compact than the 22+ ions. For the 19+ charge state as acceleration is increased to 125 V, the collision cross section assigned to the ring-like structure persists, but at 175 V decreases significantly and is consistent with a partially collapsed or buckled ring-type structure. This experiment demonstrates that imparting internal energy to 22+ ions leads to expansion of the collapsed state whereas for 19+ ions we can drive, at least partially, the structural transitions observed for the ring structure as a function of protein charge state, lending further support to our structural interpretation above.

Taken together, the data show that a native-like ring structure of TRAP subunits can be preserved in the absence of bulk water, allowing an opportunity to investigate their stability under a variety of different conditions. We found that increasing internal energy can lead to structural collapse whereas addition of tryptophan or binding of RNA enhances the overall stability of the ring. It follows, therefore, that the influence of bulk solvent on the quaternary structure of TRAP and its complexes is small in comparison with intrinsic forces within binding interfaces that stabilize the rings. Data available from x-ray analysis of the TRAP crystal structure (*28*) indicate that the inter-subunit interface corresponds to a surface area of about 1100 Å^2, dominated by a central hydrogen bonding region and flanked by two smaller areas of hydrophobic interaction. Similar interaction surfaces exist in numerous protein-protein complexes (*29*) and indicate that many assemblies may maintain their overall topology in the absence of bulk solvent, paving the way for ion mobility mass spectrometry to make significant contributions to quaternary structure determinations of large protein complexes. We anticipate that the area of structural biology most likely to benefit from the use of ion mobility separation is the analysis of protein complexes that exist in multiple functional forms in solution. As shown here, the RNA-bound complex coexists in solution with the apo form, but because they are readily separated by their *m*/*z* ratios, it is possible to characterize all components according to their overall topology. This is an important attribute given that heterogeneity is a major problem in structural biology, the potential for which increases dramatically with the size and complexity of the macromolecular complex (*30*). Current low-resolution structural biology approaches such as small angle x-ray scattering (*31*), used for determination of the shape and size of monodisperse complexes in solution, are unable to effectively characterize the chemical and structural heterogeneity that often accompanies macromolecular assemblies. Consequently, rather than determining the shape of each of the components present, most structural probes will report an average over all structures. Therefore, the ability to determine the overall topology of individual components within heterogeneous mixtures by using ion mobility coupled to mass spectrometry represents a significant advance. Moreover, knowledge of the shape of macromolecular assemblies obtained from such experiments has the potential to contribute not only to computational approaches to structure determination (*32*) but also to characterizing the transient and reversible associations that elude many existing structural biology approaches.

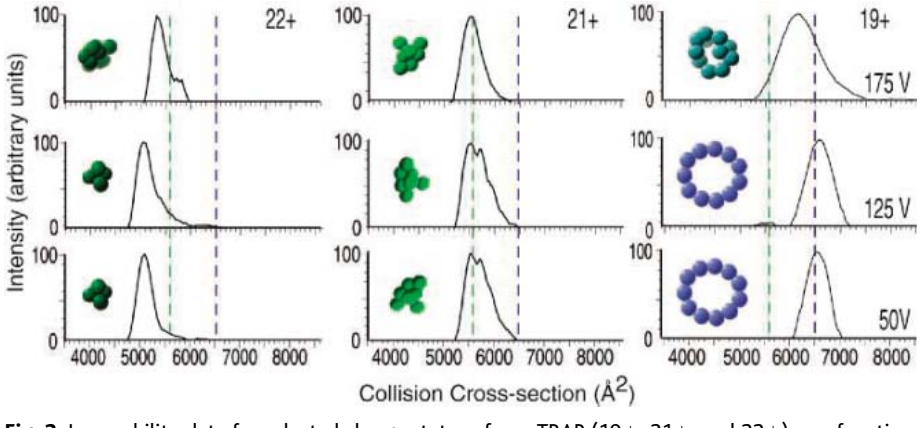

Fig. 3. Ion mobility data for selected charge states of apo TRAP (19+, 21+, and 22+) as a function of activation energy (175, 125, and 50 V) applied in the high-pressure, sampling-cone region of the instrument. The dashed lines (green and blue) represent the collision cross sections for collapsed and ring structures described in the legend to Fig. 1.

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Rapid Chiral Assembly of Rigid DNA Building Blocks for Molecular Nanofabrication

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Practical components for three-dimensional molecular nanofabrication must be simple to produce, stereopure, rigid, and adaptable. We report a family of DNA tetrahedra, less than 10 nanometers on a side, that can self-assemble in seconds with near-quantitative yield of one diastereomer. They can be connected by programmable DNA linkers. Their triangulated architecture confers structural stability; by compressing a DNA tetrahedron with an atomic force microscope, we have measured the axial compressibility of DNA and observed the buckling of the double helix under high loads.

Three-dimensional (3D) construction by self-assembly requires rigid building blocks such as tetrahedra. DNA is an ideal material for nanofabrication of rigid structures because assembly can be controlled by base-pairing (*1*) and is relatively inexpensive and simple to execute (*2*). However, DNA nanofabrication presents the problem of avoiding unwanted by-products. It is often possible to ensure that the target structure is the one that creates the largest number of Watson-Crick base pairs and is therefore the most stable product. Usually, however, there are many other possible structures that are only slightly less stable. If all component oligonucleotides are simply mixed without precaution, the yield of the target structure can be extremely low, and disordered polymeric structures can form instead. Successful strategies for the synthesis of 2D periodic structures involve a hierarchy of interactions in which preformed building blocks are linked by weaker interactions to form an array (*3*–*5*), but 3D construction is much less well developed.

Polyhedral DNA nanostructures with the connectivities of a cube (*6*) and of truncated and regular octahedra (*7*, *8*) have been made, each using a different synthetic strategy. Trisoligonucleotidyls—three oligonucleotides connected by a trifunctional linker (*9*)—have also been reported to form tetrahedra (*10*). The cube (*6*) was assembled in solution by ligation of 10 oligonucleotides, in three stages with intermediate purification steps, with 1% yield. The solid-support synthesis of the truncated octahedron (*7*) allowed greater control of the assembly process: Two halves of an edge could be joined by ligation only after a deprotection step in which a restriction endonuclease was used to cleave two precursor hairpin loops to create overlapping sticky ends. This synthesis, starting with 48 oligonucleotides, took approximately two worker-years; yield was less than 1%. Both the cube and the truncated octahedron were covalently closed catenanes that could not be disassembled without breaking covalent bonds: In designing the octahedron (*8*), this robust design principle was sacrificed to permit assembly by folding. The principal component of the octahedron, a 1.7-kb oligonucleotide synthesized using 64 synthetic oligonucleotides and amplified by cloning, was designed to have branched secondary structure; the octahedron was formed when branches folded and were bound together by intramolecular paranemic interactions (*11*).

The junctions that form the vertices of these 3D nanostructures are flexible. DNA nanostructures with triangulated architectures may be capable of resisting deformation, but their mechanical properties have not been measured. Rigidity is not enough to ensure that a DNA polyhedron has a robust and well-defined structure; it is also necessary to select one of the two possible diastereomers (enantiomers with respect to the identities of their vertices) that satisfy the pattern of connectivity imposed by the design of hybridization interactions. Discrimination between diastereomers of DNA polyhedra has yet to be demonstrated, and the stereoselectivity of the syntheses described above is unknown.

We have synthesized a family of DNA tetrahedra that have been designed to self-assemble in a single step in only a few seconds. A single diastereomer can be synthesized with yields as high as 95%. We demonstrate their versatility as building blocks for 3D nanofabrication by assembling one regular and nine different irregular tetrahedra and by connecting them with programmable DNA linkers. We then use atomic force microscopy (AFM) to image the tertiary structure of individual tetrahedra and to demonstrate their rigidity, which we exploit to measure the response of DNA to axial compression.

The DNA tetrahedron is designed to be mechanically robust; it consists of rigid triangles of DNA helices covalently joined at the vertices (Fig. 1A) (*12*). The four component oligonucleotides each run around one face and hybridize to form the double-helical edges. Four edges contain nicks (i.e., breaks in the DNA backbone) where the 5′ and 3′ ends of an oligonucleotide meet. At each vertex, adjacent edges are attached through single, unpaired "hinge" bases. In contrast to the challenging syntheses of DNA cubes (*6*) and octahedra (*7*, *8*), the synthesis of tetrahedra is extremely simple: All four oligonucleotides are combined in equimolar quantities in hybridization buffer at 95°C and then cooled to 4°C in 30 s (*13*).

Tetrahedra form with ~95% yield and migrate as single bands on a nondenaturing electrophoresis gel (fig. S1) (*13*). A covalently closed catenane may be produced by enzymatic ligation of the four nicks in the DNA backbone. We believe that the designed hierarchy of interactions between oligonucleotides contributes to the high efficiency of this one-step synthesis. We expect hybridization between oligonucleotides 1 and 2, and also 3 and 4, to form the stable, unnicked edges B and E (Fig. 1A) to occur first as the solution temperature falls. Other edges can then form cooperatively; once the formation of any other edge has linked these pairs to form a four-strand complex, all further hybridization interactions required to

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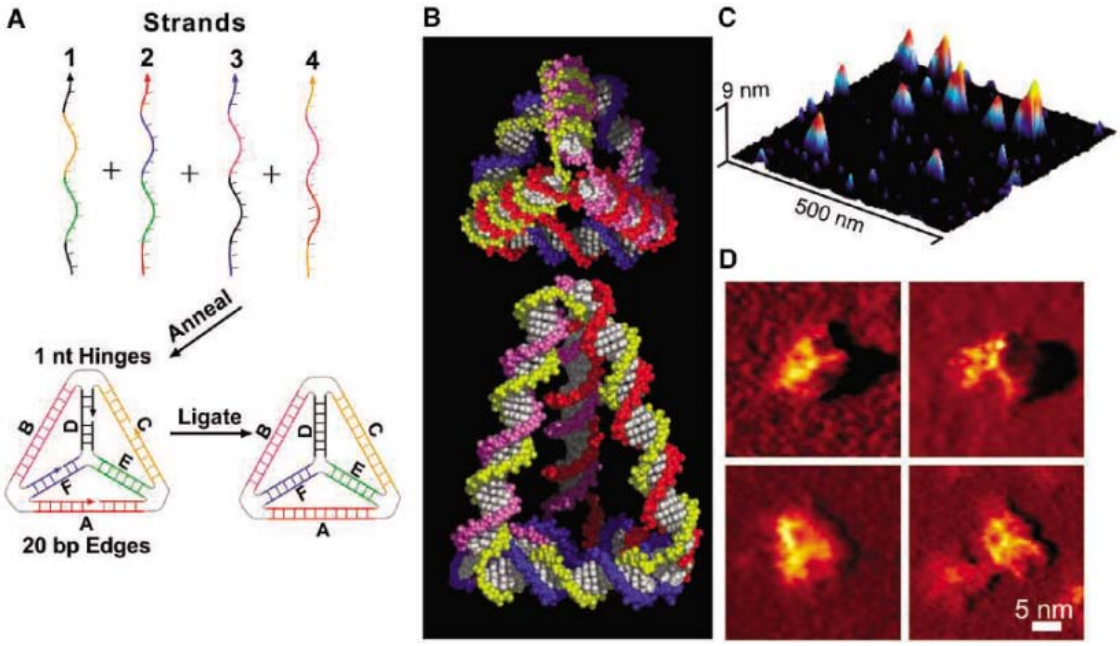

Fig. 1. DNA tetrahedra. (**A**) Design of a DNA tetrahedron formed by annealing four oligonucleotides. Complementary subsequences that hybridize to form each edge are identified by color. (**B**) Two views of a space-filling representation of a 3×20/3×30-bp tetrahedron. The backbone of each oligonucleotide is indicated by a single color. (**C**) AFM image showing several tetrahedra on a mica surface. (**D**) AFM images, recorded with ultrasharp tips, of four tetrahedra; the three upper edges are resolved.

complete the tetrahedron are intramolecular and are therefore expected to be faster than competing intermolecular interactions that would form larger complexes. The positions of the nicks are such that none of these intramolecular interactions is substantially hindered by bonds already formed.

The tetrahedra imaged by AFM in Fig. 1, C and D, were designed to have three 30–base pair (bp) edges meeting at one vertex and three 20-bp edges bounding the opposite face (a molecular model is shown in Fig. 1B). They are expected to bind to a surface in one of two orientations, with heights of ~10.5 nm if resting on the small face and ~7.5 nm if resting on any of the other three faces. Figure 1C, recorded with a tip 20 nm in radius, shows several objects with heights consistent with the two orientations. Figure 1D shows high-resolution images, obtained using ultrasharp tips with radii of only 2 to 3 nm, that resolve the three upper edges of individual tetrahedra.

To confirm that our constructs had the topology of a tetrahedron, we used selective enzymatic ligation and digestion. Incubation with T4 DNA ligase leads to ligation (covalent closure) of the nicks where the 5′ and 3′ ends of an oligonucleotide are held together in the middle of an edge, but only if the 5′ end is prepared with a terminal phosphate group. Sixteen regular 20-bp tetrahedra were formed with every combination of ligated and unligated nicks. In the denaturing gels shown in Fig. 2, A to C, linear oligonucleotides dissociated and only circular, catenated oligonucleotides were constrained to migrate together. According to the design, each ligation should produce a circular oligonucleotide and all circles produced by multiple ligations should be catenated with a linking number corresponding to the number of complete helical turns in each edge—in this case, two. The expected bands appeared when one, two, three, and four oligonucleotides were ligated (products of failed ligation were also observed). Digestion with exonuclease III, which can hydrolyze duplex DNA from a free 3′ end, confirmed

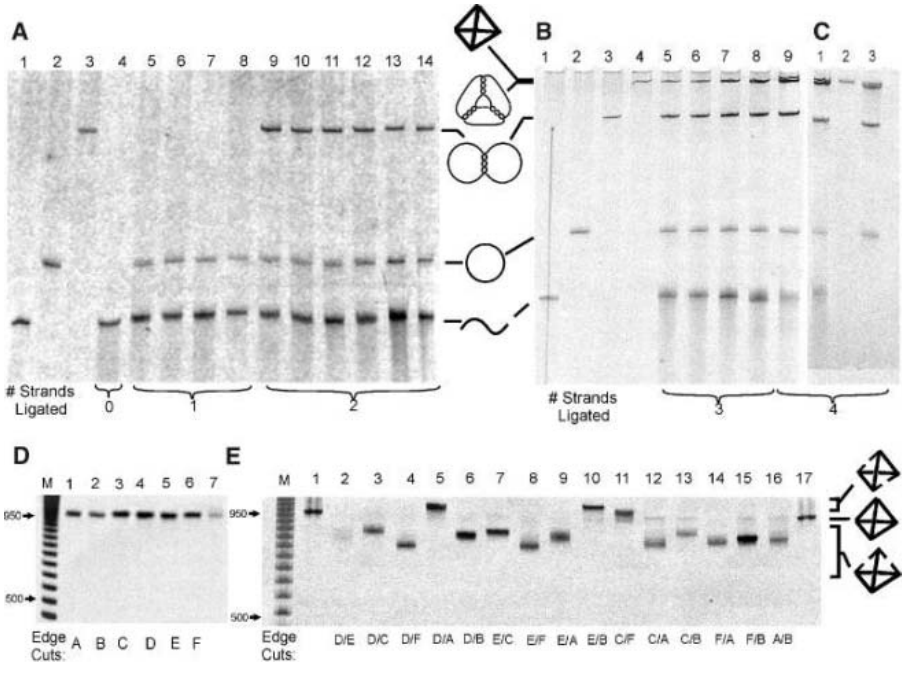

Fig. 2. Topological and structural analysis of a 20-bp regular tetrahedron. (**A** and **B**) Denaturing gels showing products of all possible combinations of ligated and unligated nicks. Control lanes contain oligonucleotides of the same length as the four components of the tetrahedron: linear (lanes A1 and B1), circular (lanes A2 and B2), and double (lanes A3 and B3) and triple (lane B4) linked circles. (**C**) Fully ligated tetrahedron (lane 1) after gel purification (lane 2) and Exo III digestion (lane 3). (**D** and **E**) Edge digestions of a fully ligated tetrahedron on a native gel. (D) Lanes 1 to 6, single cuts; lane 7, uncut tetrahedron. (E) Lanes 2 to 16, double cuts; lanes 1 and 17, uncut tetrahedron. Lane M, 50-bp ladder. See (*13*) for synthesis of markers and for keys to ligated oligonucleotides and edge-cutting enzymes.

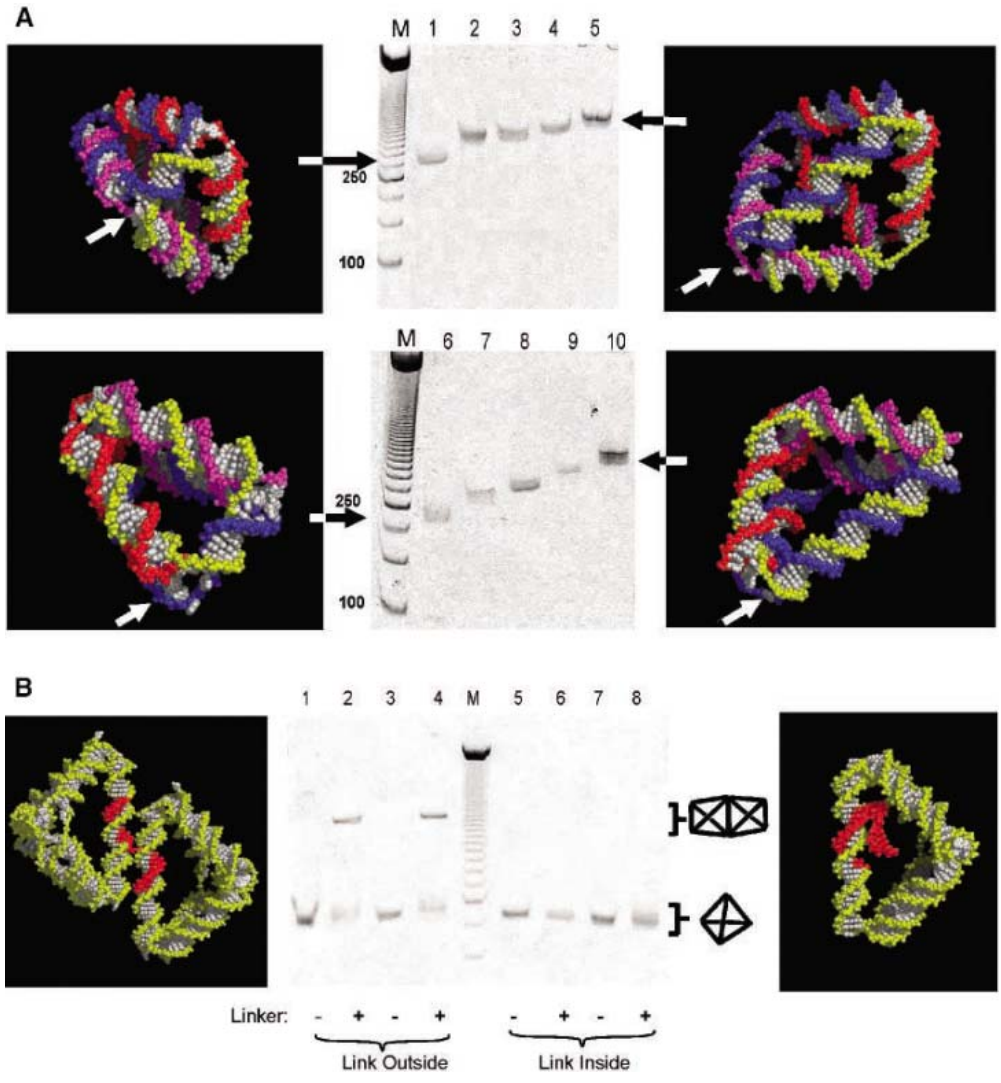

Fig. 3. Versatility and stereoselectivity of tetrahedron synthesis. (**A**) Tetrahedra with five 20-bp edges and one edge of 10 bp (lane 1), 15 bp (lane 2), 20 bp (lane 3), 25 bp (lane 4), or 30 bp (lane 5). Tetrahedra with four 20-bp edges, one 10-bp edge, and an opposite edge of 10 bp (lane 6), 15 bp (lane 7), 20 bp (lane 8), 25 bp (lane 9), or 30 bp (lane 10). For both series the tetrahedra in the first and last lanes are illustrated by 3D models; the edge that is varied is marked with an arrow. (**B**) Linking experiments demonstrating stereoselectivity. A linking strand may join two 5×20/1×30-bp tetrahedra by hybridizing in 10-bp single-stranded gaps in both long edges. There are two possible diastereomers of a DNA tetrahedron. Four gap positions, two in each strand forming the edge, were designed such that the linker would emerge on the outside of one diastereomer, accessible for further hybridization (left panel), and on the inside of the other, hindering further hybridization (right panel). A strong dimer band is observed in only the two cases consistent with the presence of the diastereomer, in which the major groove of each helix faces inward at the vertices. See (*13*) for detailed information on structures. Lane M, 50-bp ladder.

that they contained circular oligonucleotides (Fig. 2C, lane 3). The topology of the corresponding single-, double-, triple-, and quadruple-linked circles can be described using Conway's notation (*14*) as (∞), (–4), (4,4,4), and (6**13.4.13.4.13.4), respectively (fig. S2) (*13*). These results are consistent with the topology of the designed structure.

Because each edge of the tetrahedron has a different base sequence, sequence-specific enzymatic digestion can be used to provide further confirmation of the tetrahedron's tertiary structure. Each edge was designed to contain a different restriction sequence that may be digested (cut) by one of six restriction endonucleases. The effects of edge digestion on a fully ligated tetrahedron are shown using native gels in Fig. 2, D and E. None of the six possible single-edge cuts, not even the blunt cut produced by Alu I (lane 1), had a measurable effect on the tetrahedron's mobility (Fig. 2D). We conclude that the tetrahedron's tertiary structure is particularly stable. The products of each of the 15 possible double-edge digests are shown in Fig. 2E. Three of the cuts created a band with lower mobility than the uncut band; the remaining 12 cut bands had higher mobility. The two groups correspond to two distinct ways of cutting the tetrahedron twice: Higher mobility bands were created by cuts on adjacent edges and lower mobility bands by cuts on opposite edges, confirming the designed relations between edges.

Our assembly method is extremely flexible. Figure 3A shows two series of tetrahedra made with four 20-bp edges; a fifth edge of 20 or 10 bp, respectively; and a sixth edge, opposite the fifth, that varied in length between 10 and 30 bp. Each synthesis resulted in a single-band product whose mobility decreased with increasing edge length. We can also adapt the design to introduce nicks into all six edges (fig. S3) (*13*); single-stranded overhangs at these nicks could be used to create sticky ends to join tetrahedra to make 3D structures.

We have investigated an alternative linking strategy based on the incorporation of a single-stranded gap in a tetrahedron edge (Fig. 3B); oligonucleotides containing two subsequences, each capable of hybridizing in a gap, can be used to link tetrahedra in a programmable manner. A linking strand containing two identical subsequences joins preformed tetrahedra to create homodimers as expected (Fig. 3B, lanes 2 and 4) (fig. S4) (*13*). We have also used linkers incorporating two different binding sequences to create heterodimers (fig. S5) (*13*).

Dimer formation was used to investigate the stereoselectivity of the synthesis. The gapped edge is not free to rotate: The position of the gap along the edge determines the azimuthal position of the free end of the hybridized linker, and thus whether it can reach and hybridize with another tetrahedron. Two gap positions were designed, one for each of the two strands forming the edge, such that the linking strand would project away from the center of one diastereomer but

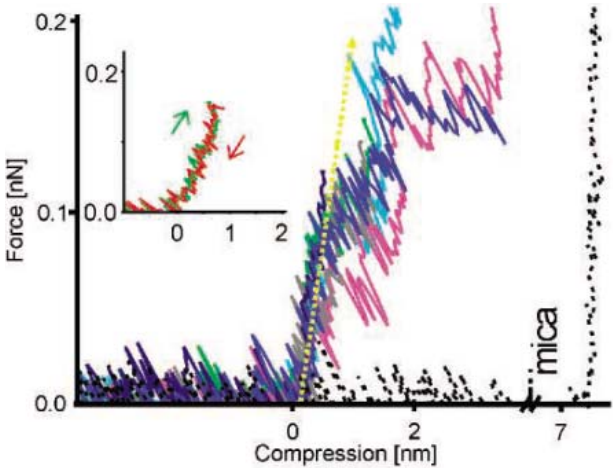

Fig. 4. Compression of single DNA tetrahedra. Compression curves show linear elastic response up to a load of 0.1 nN. At higher forces, most tetrahedra deform irreversibly. Offsets were adjusted to overlap the linear parts of the seven curves. Inset: Reversibility of the elastic response of a typical tetrahedron.

into the center of the other (Fig. 3B, outer panels). In the latter configuration, the linker is expected to be inaccessible. Controls with gaps translated by five bases (half a helical turn) were designed to have the opposite linker orientation. The results of linking experiments for a tetrahedron with 5×20/1×30-bp edges (Fig. 3B) are consistent with the presence of a large excess of the diastereomer in which the major groove of each helix faces inward at each vertex, indicating a significant difference between the formation rates or stabilities of the two possible diastereomers. Stereoselective synthesis, in combination with structural rigidity, ensures that the relative coordinates of any part of the structure can be defined with near-atomic accuracy, an essential property of a nanostructure to be used as a building block for molecular nanofabrication.

We used these structurally braced tetrahedra to investigate the behavior of DNA under compression. Although DNA under tension has been widely studied (*15*–*18*), DNA strands of micrometer length buckle at extremely low forces. Measurement of the response of DNA to large compressive loads could help to resolve the current controversy over the nature of structural changes associated with rare large-angle deformations of the double helix (*19*, *20*). To measure the mechanical response of a single tetrahedron directly, we used an AFM tip as a sensitive force transducer. The tip was centered over a tetrahedron located in imaging mode and was then moved toward the surface while recording force. Compression curves for seven distinct 3×20/3×30-bp tetrahedra, as imaged in Fig. 1, are shown in Fig. 4. For forces up to ~100 pN, the response was approximately linear and reversible (Fig. 4, inset) with an average force constant of 0.18 (±0.07) N m^{-1}. At higher forces, the response was nonlinear and varied from tetrahedron to tetrahedron; tetrahedra generally softened suddenly and deformed irreversibly at a load between 70 and 200 pN.

To model the compressibility of a DNA tetrahedron, we treat its edges as elastic rods pinned (freely hinged) at the vertices. The calculated response of a 3×20/3×30-bp tetrahedron to a compressive load applied between the top vertex and the surface supporting the bottom face is approximately the same for both orientations and is dominated by axial compression of the upstanding edges. The calculated force-displacement (F-d) curve is approximately linear up to a critical load at which the tetrahedron buckles. The boundary conditions at the bottom face have a small effect on the response: If the bottom vertices are not fixed but allowed to slide on the surface, then the bottom edges stretch and the overall stiffness of the construct is reduced by ~3% and ~13% for the tall and short orientations of the tetrahedron, respectively. From the gradient of the linear part of the measured F-d curve, we infer an elastic modulus of K_c = 0.7 (±0.3) nN for one DNA double helix in compression. In the linear response regime, elastic moduli measured by extension and compression should be equal; our value for K_c is near that of the elastic modulus of DNA in tension, K_e ~ 1.1 nN, obtained by fitting the force-extension curves of DNA duplexes (*17*, *18*). Our direct measurement of the axial elastic response of DNA in compression was made possible by the braced structure of the tetrahedron that enabled a short DNA helix to bear a compressive load without bending or tilting.

We can use our measured elastic modulus to estimate the load at which we would expect the edges of a tetrahedron to buckle. If a DNA duplex is modeled as a uniform cylinder of radius r = 1 nm (*21*), then the critical compressive force in an edge at which we would expect Euler instability is $F_c = \pi^2 r^2 K/(2\upsilon l)^2$, where K is the elastic modulus, l is the edge length, and υ is a numerical factor that depends on the boundary conditions at the vertices. If the vertices are pinned, then υ = 1; if the orientations of the edges at the vertices are fixed, then υ = ½. The corresponding AFM tip loads lie in the range from 50 to 300 pN, which is consistent with the range of loads at which tetrahedra were observed to soften suddenly. Our observations of the failure of tetrahedra under high load can thus be explained on the basis of the traditional model of uniform DNA bending (*20*); this result is consistent with our interpretation that the linear part of the F-d curve is caused by pure axial compression of the tetrahedron's upstanding edges before buckling occurs.

The structural changes associated with DNA bending are the subject of controversy. Suggestions that sharp bends due to local melting or kinking (*22*) are observed in DNA cyclization experiments (*19*, *23*, *24*) are countered by measurements that indicate that the probability of such kinks is very low (*20*). Extended observation of tetrahedra under compression may be a useful method for investigating the energy and sequence dependence of inhomogeneous bending and of the effects of compressive strain on DNA-protein interactions.

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The Chemistry of Deformation: How Solutes Soften Pure Metals

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Solutes have been added to strengthen elemental metals, generating usable materials for millennia; in the 1960s, solutes were found to also soften metals. Despite the empirical correlation between the "electron number" of the solute and the change in strength of the material to which it is added, the mechanism responsible for softening is poorly understood. Using state-of-the-art quantum-mechanical methods, we studied the direct interaction of transition-metal solutes with dislocations in molybdenum. The interaction increases dramatically with increasing electron number and strongly influences the mechanisms responsible for plasticity in these materials. Our quantitative model explains solution softening of metals by using changes in energy and stress scales of plasticity from solutes.

Solutes have played a key role in producing useful materials from pure metals over the past millennia, driving technological advances in civilization—from the Bronze Age to the Iron Age to the industrial revolution. For most of human history, alloying was used to increase the strength of metals (*1*). Four decades ago, a wealth of evidence showed that for some body-centered cubic (bcc) metals, solutes could decrease material strength (*2*). This effect, known as solid-solution softening, was observed as a reduction in the stress at which a material begins to deform irreversibly (yield stress) or as a reduction in the material's ability to resist indentation (hardness). Softening is important for producing viable materials: The bcc refractory metals (Nb, W, Ta, and Mo) offer a possible new class of high-temperature materials for components used in turbine engines or nuclear power plants, but the metals have poor low-temperature behavior in elemental form. As the temperature decreases from 15% of the melting temperature (above room temperature for refractory metals) down to absolute zero, strength increases rapidly. This high strength is undesirable, because it is linked with an increase in fracture and low malleability, ultimately limiting the use of these materials as critical structural components. A classical metallurgical practice is to reduce this risk by incorporating solid-solutions or by introducing new softer phases. Models have only succeeded in qualitatively explaining the possibility of low-temperature softening (*3*–*5*) or in finding empirical correlations to deduce scaling trends (*6*). Moving beyond these empirical techniques requires a combination of chemistry, materials physics, and large-scale computation to investigate how solute chemistry changes deformation: the "chemistry of deformation."

Irreversible plastic deformation of metals is controlled by dislocation defects, and solute-induced softening is controlled by interactions of solutes and dislocations. Dislocations are topological line defects that move at stresses below the stress required to irreversibly deform a dislocation-free crystal (*7*). In bcc metals, low-temperature plastic deformation is controlled by moving straight screw-character dislocations. A dislocation line moves perpendicular to its length by nucleating a pair of opposite-directed "kinks." These migrate away from each other along the dislocation, moving the dislocation line forward to the next lattice site like the locomotion of a snake. Solute chemistry affects double-kink nucleation and kink migration to produce both softening and hardening.

Our model explains the following experimental data for a Mo-Re alloy, which is the classic solid-solution softening system. Below a temperature of 350 K, Mo-Re is softer than pure Mo for small Re concentrations (*8*). Softening continues up to 16 atomic %, where the alloy becomes harder than pure Mo. The maximum softening occurs at 8 atomic % at 77 K, and the maximum softening concentration decreases as temperature is increased (*9*). Thus, a given solute concentration can soften an alloy at one temperature and harden at another; and at a given temperature, increasing solute concentration can first soften and then harden the alloy at higher concentrations. Similar features appear for other 5d-row solutes with higher d electron numbers (Os, Ir, Pt), but the maximum softening occurs at much smaller concentrations. Metals with lower d electron numbers (Hf, Ta) harden for all concentrations and temperatures. The goal of alloy design for Mo alloys is to soften the low-temperature behavior, reducing the risk of fracture.

We show here that the prediction of strength with changing alloy concentration and temperature for Mo alloys requires calculation of the direct solute-dislocation interaction and modeling of those effects on plasticity. State-of-the-art quantum-mechanical electronic structure methods (*10*–*13*) with special dislocation boundary conditions (*14*) calculate the interaction energy between a single straight dislocation and a solute and the change in the resistance to the motion of the dislocation. These data enter a solid-solution softening model of plasticity by changing energy and stress scales of double-kink nucleation and kink-migration enthalpy barriers. The effect of random clustering (where more than one solute atom interacts with a kink) is crucial in modeling changes in kink migration above the dilute limit. Also, the bonding environment near a dislocation is distinct from the bulk, producing the unique chemistry of deformation. Our model quantitatively predicts strength measurements of Mo-Re and matches hardness measurements of Mo-Pt, two systems with dramatically different softening and hardening behavior. The details of the computational methods are included in (*15*).

As a starting point, Fig. 1 compares the nearest-neighbor geometry of bulk bcc Mo to that of a 1/2[111] screw-character dislocation. Viewed along the [111] direction, the bulk cubic structure forms a triangular lattice of atomic rows; the triangles can be viewed as spirals of alternating chirality. To form a dislocation, the chirality of a triangle is changed by displacing each row in the triangle by different amounts

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along the [111] direction (out of the page). The change of one triangle affects its neighbors, with local displacements dying off as the inverse distance from the dislocation center. Although this geometry maintains the nearest-neighbor coordination of a bcc lattice throughout, the bond states near the dislocation are distinctly different from those in bulk Mo.

Our solid-solution model is based on thermally activated motion of dislocations by double-kink nucleation and kink migration (*3*, *4*, *15*–*17*). Double-kink nucleation is the rate-limiting process at low temperatures, and kink migration is rate-limiting at higher temperatures. Stress σ (resisting force per area) is measured against applied strain ε (elongation) at a constant strain rate $\dot{\varepsilon}$. The Orowan equation (*18*) connects $\dot{\varepsilon}$ to the motion of dislocations at yield $\dot{\varepsilon} = b\rho_m \bar{v}_{disl}(\sigma)$, where b is the Burgers vector length, ρ_m is the mobile dislocation density per area, and $\bar{v}_{disl}$ is the average dislocation velocity with stress. The average dislocation velocity is the distance a dislocation moves because of a kink (by geometry, $0.94b$) divided by the average time to make stable double kinks and migrate the entire dislocation. Thus,

$$\dot{\varepsilon} = 0.94b^2\rho_m \times\left[(\text{nucleation rate})^{-1} + (\text{migration rate})^{-1}\right]^{-1}$$

where the rates are thermal activation rates, (attempt frequency) $\times$ exp[$-$(enthalpy barrier)/(k_BT)], where k_B is Boltzmann's constant and T is temperature, and the enthalpy barriers decrease with stress. This equation is solved numerically for the yield stress at a given strain rate, temperature, and solute content. The enthalpy barriers have an energy and a stress scale, and solutes affect both scales.

The stress scales are connected to the Peierls stress, which is the critical applied stress where a dislocation moves, producing plastic deformation and relieving stress. The Peierls stress of pure Mo at 0 K has been previously calculated by applying a stress and monitoring the motion of atomic rows of the dislocation (*14*). A screw-character dislocation moves to the right (i.e., the [11$\bar{2}$] direction) by displacing atomic rows along [111] to change chirality (Fig. 1). The atomic row at the bottom right of the core upward-pointing triangle moves out of the page by 1/6[111] to change its spiral from counter-clockwise (CCW) back to clockwise (CW), and the remaining two rows of the new core upward-pointing triangle to the right change chirality from CW to CCW. Thus, the Peierls stress is correlated to the stiffness for moving a single atomic row in the dislocation core, and changes in this stiffness from solutes change the stress scale in the enthalpy barriers in our solid-solution model.

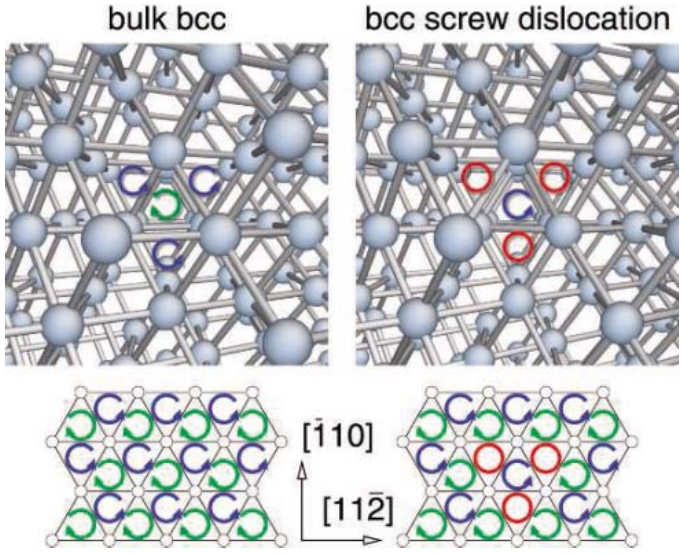

Fig. 1. Atomic nearest-neighbor geometry of a bcc 1/2[111] screw-character dislocation in Mo extending out of the page (**right**) compared with bulk bcc Mo (**left**). A bcc crystal can be viewed as atomic rows coming out of the page arranged in a triangular lattice. The upward-pointing triangles of three atomic rows spiral out of the page with clockwise chirality (CW arrow) and with counter-clockwise chirality (CCW arrow) for downward-pointing triangles. CW spirals must share edges with CCW spirals and vice versa. A screw-character dislocation is formed by changing chirality of one upward-pointing triangle. The three neighboring, downward-pointing triangle spirals flatten in the plane, removing any chirality (marked as open circles). These changes come from displacements of atomic rows out of the page. The four highly modified triangles form the "core" of the dislocation. The remaining triangles keep their initial chirality, becoming more bulklike further from the core. This figure was produced using ATOMEYE (*19*).

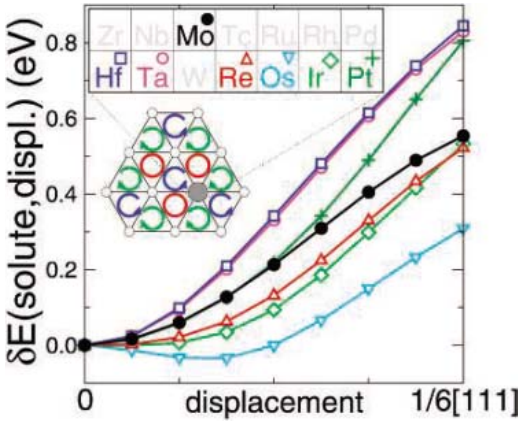

Fig. 2. The change in energy from displacement of an atomic row in the core of a Mo dislocation for different solutes substituted into that row. The inset dislocation core schematic identifies the displaced row in gray. The solid circles indicate the energy for a row of pure Mo; the remaining curves give the energy for a row in the core containing a solute atom. Energies are relative to the relaxed core with the respective solute. The curvature at zero displacement is the stiffness for moving a row in the dislocation core; differences in stiffness change the Peierls stress.

Different solutes change the energy to displace an atomic row in the core of a 1/2[111] screw-character dislocation (Fig. 2). Solutes having lower d electron numbers (Hf and Ta) increase the stiffness (the curvature at zero displacement, table S1) (*15*), which we infer strengthens the Mo alloy, whereas those having higher d electron numbers (Re, Os, and Ir) decrease the stiffness, leading to softening. The exception to this trend is Pt, which shows a small change in stiffness relative to pure Mo. However, Mo-Pt is known experimentally to be softer than pure Mo for small Pt concentrations. The inability of the change in stiffness (which we define as the Peierls misfit) to explain softening implies an additional solute-dislocation interaction is responsible.

The energy scales are connected to the direct solute-dislocation core interaction (Fig. 3). The energy profile is defined relative to a widely separated dislocation-solute pair, and E_{int} is defined as the maximum interaction energy (table S2 shows all solutes) (*15*). Re shows a weak, short-range interaction, but it has a larger Peierls misfit than does Pt. The weaker interaction and larger Peierls misfit of Re produces a small softening effect; but these effects increase at high concentrations, where multiple solutes interact with the dislocation. The large attractive interaction of Pt produces a substantial change in the energy scale and strong initial softening, but leads quickly to hardening at higher concentrations.

Solutes modify double-kink nucleation by changing the nucleation barrier along

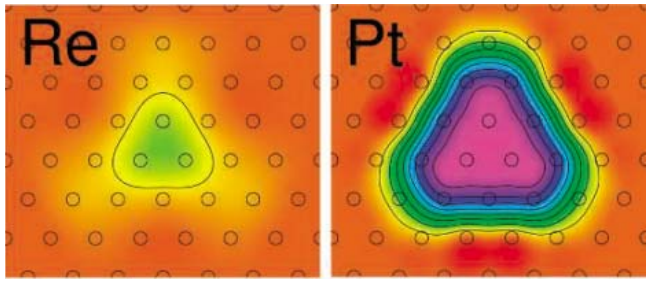

Fig. 3. Solute-dislocation interaction-energy profile for Re (**left**) and Pt (**right**) in Mo. The contours are at 0.1-eV intervals, and the interaction is attractive for all sites. Each circle is a possible lattice site for a solute atom in an atomic row; the dislocation is located in the center of the profile. The Pt dislocation interaction is stronger and has a longer range than Re. The interaction energy E_{int} is the maximum value in the profile.

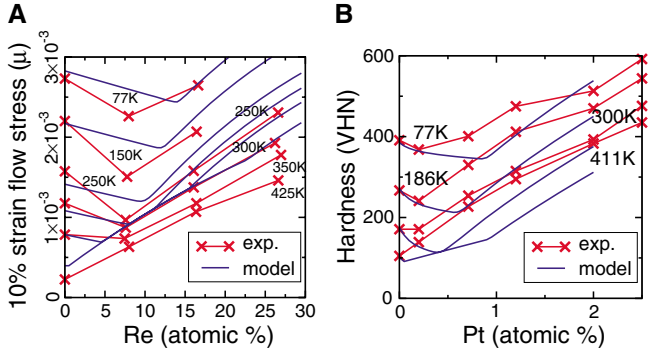

Fig. 4. Predicted strength for Mo-Re and Mo-Pt as a function of solute concentration for different temperatures, compared with experiments. (**A**) Flow stress at 10% strain for Mo-Re and experiments (exp.) of (*8*). The flow stress is scaled to the shear modulus μ = 139 GPa. (**B**) Vickers hardness number (VHN) for Mo-Pt and experiments of (*9*).

the entire length of dislocation and by locally modifying the barrier at solute sites. Solutes change the stiffness for dislocation motion, producing a global change in the stress scale for double-kink nucleation. Locally, an average c possible nucleation sites are occupied by a solute, whereas $(1 - c)$ are not. The change in the nucleation energy scale from the solute is the solute-dislocation interaction energy E_{int}. Attractive solute interactions and negative Peierls misfits (Re, Os, Ir, and Pt) increase nucleation of double kinks and provide more favorable nucleation sites, which leads to softening at low temperatures.

The rate-limiting step in kink migration is the time to overcome the largest solute cluster on the dislocation line (*16*). The size of the largest cluster encountered (assuming a random distribution of solutes) is $25\sqrt{c}$, where the prefactor depends weakly on the dislocation density and kink width (fig. S2) (*15*). This gives a cluster size of 1 solute for c = 0.16 atomic %, and 8 solutes for c = 10 atomic %. Kinks in pure bcc metals are very mobile, so any solute interaction impedes the motion of kinks. Thus, we write the solute barrier energy scale as $25\sqrt{c|E_{int}|}$, slowing kink migration and producing hardening at higher temperatures and concentrations.

The predicted strength for Mo-Re and Mo-Pt with changing solute concentration for several temperatures compared with experiment is shown in Fig. 4. The predicted value of flow stress and hardness for pure Mo was fit to the experimental data (figs. S1 and S3) (*15*). The attractive interaction of Re leads to softening for low solute concentrations because of increased double-kink nucleation. As the concentration increases, there is a crossover to kink-migration–limited flow stress, which hardens with additional solute. The crossover happens at lower concentrations for higher temperatures, because kink migration becomes more important than double-kink nucleation at higher temperatures. Qualitatively, the same softening behavior is seen for Pt as for Re: softening initially for low concentrations and crossing over to hardening at higher concentrations. The crossover concentration decreases with increasing temperature. However, the concentration scales differ by an order of magnitude. Even though Mo-Re and Mo-Pt differ dramatically in scale, a single model can capture the key physics of both systems.

Our model for solid-solution softening and the computation of interaction parameters requires careful treatment of the dislocation geometry and chemistry, as well as the statistics of clustering. The geometry of the dislocation core creates a bonding environment that is distinct from the bulk. In fact, using classical bulk approximations can produce erroneous results (hardening versus softening) or mechanisms (interaction energy versus Peierls misfit). Statistical modeling of the solute distribution is needed to produce the clustering effect important for the hardening of Mo-Re at high solute concentrations. Without clustering, the Re-dislocation interaction is too small to produce hardening effects.

Our model and calculation of the interaction parameters explains the softening and hardening of Mo by Re and Pt over a range of concentrations and temperatures. Direct solute-induced changes to energy and stress scales of double-kink nucleation and kink migration are sufficient, when coupled with the correct interaction parameters, to quantitatively predict experimental observations. The calculation of the interaction uncovers underlying electronic effects that we are now able to access by using current tools and computational resources. Our approach connects ab initio atomic-level interactions and mesoscopic mechanical behavior to explain the chemistry of deformation. Such an approach can also be applied to solute-induced softening in other technologically important materials, such as Fe and Nb.

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Rapid Glacial Erosion at 1.8 Ma Revealed by $^4He/^3He$ Thermochronometry

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Alpine glaciation and river incision control the topography of mountain ranges, but their relative contributions have been debated for years. Apatite $^4He/^3He$ thermochronometry tightly constrains the timing and rate of glacial erosion within one of the largest valleys in the southern Coast Mountains of British Columbia, Canada. Five proximate samples require accelerated denudation of the Klinaklini Valley initiating 1.8 ± 0.2 million years ago (Ma). At least 2 kilometers of overlying rock were removed from the valley at ≥5 millimeters per year, indicating that glacial valley deepening proceeded ≥6 times as fast as erosion rates before ~1.8 Ma. This intense erosion may be related to a global transition to enhanced climate instability ~1.9 Ma.

The hypotheses that alpine glaciers erode at higher rates than rivers (*1*, *2*) and control mountain topographic relief (*3*, *4*) can be tested if pre- and syn-glacial erosion rates can be measured. Debate over the relative contributions of fluvial and glacial erosion to the development of relief has persisted in part because glacial erosion rates have proven difficult to measure, and because it is not well known when and how fast relief develops. Recent advances in quantifying glacial erosion processes include studies of sediment accumulation rates (*5*), suspended sediment loads (*6*), geochronology (*7*–*9*), and numerical modeling of subglacial processes (*10*–*12*). These studies have led to an apparent discrepancy between erosion rates determined from sediment yields (*5*) (on time scales $<10^3$ years) and erosion rates inferred from low-temperature cooling ages (*8*). The latter are sensitive to mean erosion of mountain ranges over much longer time scales ($>10^6$ years) and usually indicate slower rates of erosion than those determined from sediment yields. A critical evaluation of the long-term consequences of glaciation on topography has been hampered by the lack of data to constrain erosion rates before, and during, past glaciations. We present an application of $^4He/^3He$ thermochronometry (*13*) to compare long-term erosion rates before and during alpine glaciation in the Klinaklini valley of the Coast Mountains, British Columbia.

The thermal field of the uppermost few kilometers of Earth's crust responds to changes in surface topography (*14*). Consequently, the history of mountain relief is recorded by the cooling history of rocks as they approach the surface via denudation. (U-Th)/He ages of apatite provide the most sensitive indicator of such near-surface cooling (*14*). This sensitivity arises from the temperature dependence of helium diffusion: The ^4He concentration in a cooling apatite reflects radiogenic production and diffusive loss integrated along the cooling path from ~80°C, where ^4He retention effectively begins, to ~20°C, where retention is nearly quantitative. The (U-Th)/He age of an entire crystal is usually interpreted as the time elapsed since the apatite crossed the ~70°C isotherm (*15*). However, far more detailed information on the cooling path, essential to resolving the role of glacial incision, potentially resides in the spatial distribution of ^4He within a grain.

In a sample containing a uniform distribution of proton-induced ^3He (*16*), sequentially measured $^4He/^3He$ ratios during stepped-extraction document the spatial distribution of radiogenic ^4He (*17*, *18*). When combined with a (U-Th)/He age and helium diffusion kinetics, the ^4He distribution quantitatively constrains the sample's cooling path (*13*, *19*). We applied this method in the Coast Mountains, which extend for ~1000 km along the western margin of North America and have up to 4 km of topographic relief. Previous thermochronology results suggest that mountain building and exhumation >0.5 mm/year began ~10 Ma in this region (*20*). Although this mountain range was heavily incised by glaciers, the timing and magnitude of glacial erosion are only

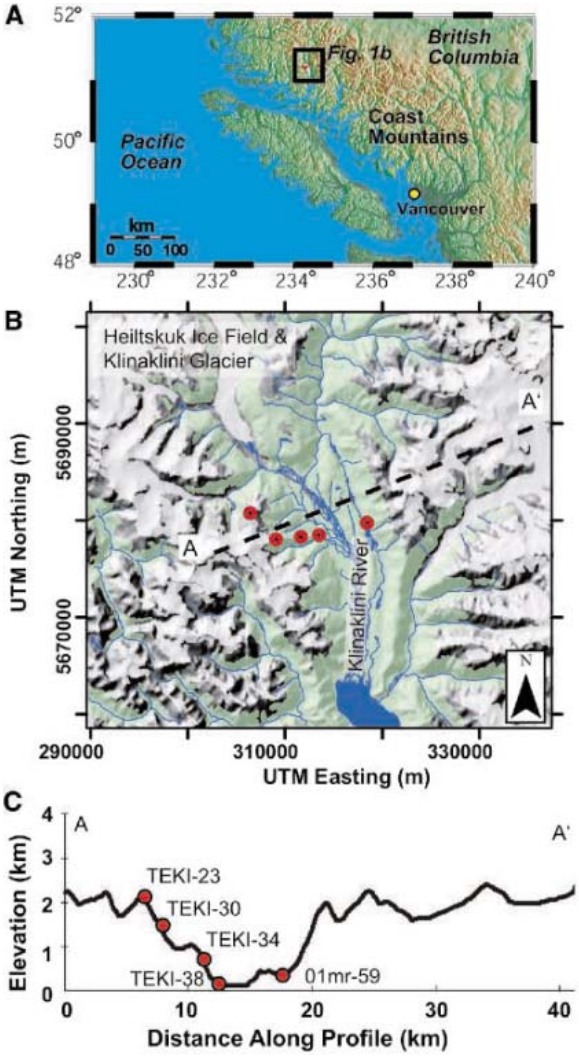

Fig. 1. Topography and sample location maps. (**A**) Regional physiography. Black box represents area shown in (B). (**B**) Shaded relief topography, vegetation cover (green), present-day glacial extent (white to light gray), sample locations (red), and topographic profile location across the Klinaklini valley (A-A′). (**C**) Topographic profile and sample elevations projected onto profile A-A′.

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poorly known (*9*, *20*, *21*). We report ^{4}He/^{3}He thermochronometry results for five apatite samples separated from granitic rocks collected along an approximately vertical transect in the ~2.5-km-deep, U-shaped Klinaklini valley (Fig. 1). This valley is one of many similarly shaped glacial valleys and fjords draining the western side of the southern Coast Mountains. Samples were collected 10 km downstream from the confluence of the present-day Heiltskuk Icefield and Klinaklini glacier (~800 km^2) and a former alpine ice sheet of equal or greater size present in the main Klinaklini river valley during the last glacial maximum (*22*) (Fig. 1). From our observations of glacial trim lines, we estimate maximum ice thicknesses of ~2.5 km at this location.

The (U-Th)/He ages of the five samples range from 1.7 to 6.4 Ma. Sample 01MR-59, collected near the Klinaklini valley floor, has the youngest (U-Th)/He age (1.7 ± 0.1 Ma), so its ^{4}He distribution constrains recent thermal perturbations with the highest resolution. Figure 2 is an example of the ^{4}He/^{3}He thermochronometry results for this sample. Details of the other four samples are presented in (*18*) and discussed later. Collectively, these results quantify the helium diffusion kinetics and reveal the spatial distribution of ^{4}He within each sample.

Using the diffusion kinetics quantified from Fig. 2A (*23*), Fig. 2B shows three model cooling paths that produce the (U-Th)/He age observed for sample 01MR-59, yet different spatial distributions of ^{4}He (Fig. 2C). Ejection of α particles from the outer ~20 μm of a mineral confers a predictable shape to the radiogenic ^{4}He distribution, which is independent of diffusion (*13*, *24*). The ^{4}He distribution inferred from the data shown in Fig. 2C is almost entirely explained by α-ejection, contains little diffusive signal (red curve), and requires rapid cooling. In contrast, the ^{4}He/^{3}He measurements clearly preclude thermal histories involving monotonic cooling below 80°C throughout the Pleistocene (green curve).

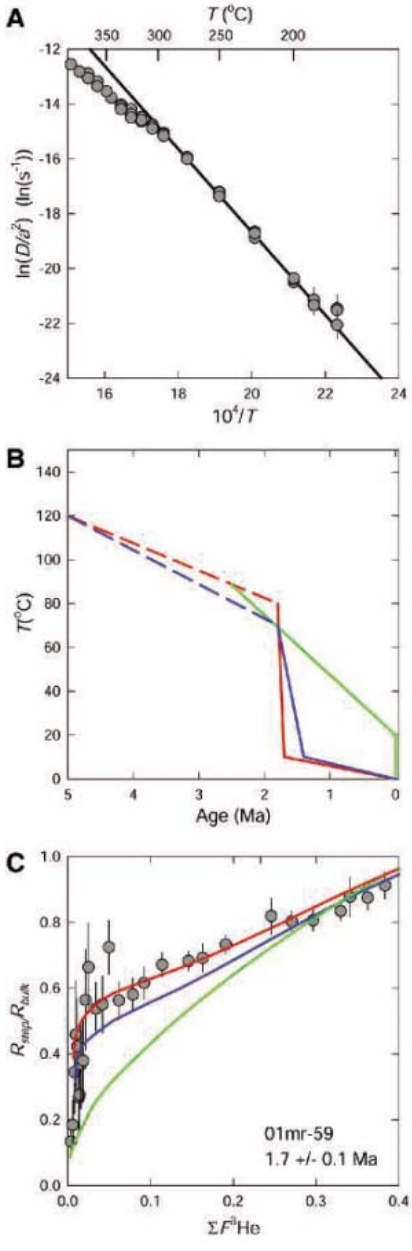

Fig. 2. ^{4}He/^{3}He thermochronometry for apatite sample 01MR-59. (**A**) ^{3}He diffusion Arrhenius plot; circles are the diffusion coefficients, *D*, normalized to the diffusive length scale, *a*, calculated (*38*) from release fractions of proton-induced ^{3}He (*16*). Solid black line is the inferred helium diffusion kinetics for 01MR-59 used to construct models shown in (B) and (C), determined by linear regression to a subset array (includes the 175° to 295°C steps; n = 22). Steps deviate from linearity above 300°C because of a change in diffusion mechanism (*36*), which may not apply to lower temperatures relevant to our models and are therefore excluded from the regression. (**B**) Model cooling paths. Each of these models yields the observed (U-Th)/He age for 01MR-59 (1.7 ± 0.1 Ma). Dashed lines are unconstrained by this sample. (**C**) Ratio evolution diagram. Shown are measured isotope ratios for each release step, R_{step} (R = ^{4}He/^{3}He), normalized to the bulk ratio R_{bulk}, plotted versus the cumulative ^{3}He-release fraction, ΣF^3He. Three models are shown that correspond to the cooling paths in (B). Error bars (1σ) are specified by a vertical line through each point. The best-fitting model is shown in red; the blue curve estimates the minimum cooling rate allowed by the ^{4}He/^{3}He data and provides a confidence limit on the rapid cooling event at 1.8 Ma.

Of the models in Fig. 2, the best fit (red curve) implies that rapid cooling began ~1.8 Ma. Because the ^{4}He/^{3}He data are consistent with an end-member ^{4}He distribution (i.e., no diffusion), they place a stringent restriction on the possible cooling path of the sample. To illustrate this limit, and to estimate a confidence interval for the solution, we sought a lower bound on the cooling rate the sample could have experienced. The blue curve in Fig. 2C shows a lower limit at which point the model is clearly no longer in agreement with the observations, requiring cooling from at least ~70°C at 1.8 Ma to below 20°C by ~1.4 Ma. Therefore, for 01MR-59, the red and blue curves in Fig. 2 define a confidence interval on the cooling path; both demand very rapid cooling denudation beginning 1.8 ± 0.2 Ma.

Widespread gradual climate change to ice-house conditions initiated ~2.7 Ma (*25*), whereas between 1.9 and 1.7 Ma clear evidence exists for a global transition to increased climate variability (*26*), major changes in the provenance of Northern Hemisphere erosion products (*27*, *28*), and the establishment of coldwater upwelling conditions in the tropical and subtropical eastern Pacific ocean (*26*). These global trends in climate are consistent with intense erosion ~1.8 Ma, a time when large ice sheets with a high potential for erosion were likely pervasive across the Coast Mountains and major increases in ice-rafted debris are observed in sea-sediment records (*29*). Thus, glacial erosion within the valley is the most plausible way to explain such rapid cooling of the rocks. Measured geothermal gradients in the region range between ~20° and 30°C/km (*30*, *31*). Assuming these gradients are representative of the thermal field at the time sample 01MR-59 cooled below 80°C, our results imply that ~1700 to 2200 m of overlying rock was rapidly eroded. Adopting the blue curve in Fig. 2B as a lower bound on the cooling rate of 01MR-59, the implied erosion rate was ≥5 mm/year between 1.8 and 1.4 Ma. These results also imply ≤300 m of erosion within the valley since 1.4 Ma.

An erosion event of this magnitude must have affected samples in a broader region, although the magnitude of erosion could be spatially variable. Application of ^{4}He/^{3}He thermochronometry on multiple, neighboring samples provides a test for internal consistency and a way to bootstrap solutions and develop a three-dimensional denudation record through time. For example, assuming that thermal gradients between samples were always ≤30°C/km, a best-fit cooling path for one sample restricts the acceptable cooling path of a second sample located 500 m (vertically) to be offset by no more than 15°C at all times. We tested the internal consistency of our results using a vertical profile of samples collected ~6 km from sample 01MR-59 (Fig. 1).

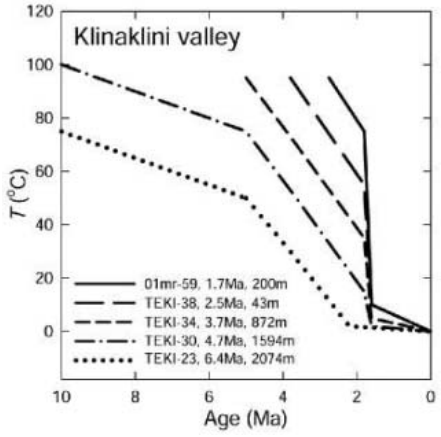

Fig. 3. Internally consistent set of cooling paths for a near-vertical array of samples collected from the west wall of Klinaklini valley. Listed in the legend are the name, (U-Th)/He age, and elevation of each sample, respectively. The corresponding ^{4}He/^{3}He thermochronometry results are shown in the supporting online material. Confidence intervals for each cooling path are approximately the same as that indicated by the difference between the red and blue curves in Fig. 2.

Figure 3 shows a set of cooling paths for four apatite samples collected from the western wall of the valley (Fig. 1) along with the solution for 01MR-59. All of the ^{4}He/^{3}He thermochronometry results (*18*) support the cooling history inferred from 01MR-59 and suggest that samples collected deep within the Klinaklini valley (at present elevations ≤2000 m) experienced rapid cooling, starting ~1.8 Ma. The four samples from the western wall require an earlier period of slower cooling (~20°C/10^6 years), between 5 and 2 Ma, and the two highest samples suggest even slower cooling before 5 Ma. As expected, the data require that samples at higher elevations were at lower temperatures, and therefore closer to the paleo-surface, as the Klinaklini valley deepened.

For instance, the data require that by 1.8 Ma, sample TEKI-23 was already at temperatures <20°C, and so was located very near the paleo-surface. Therefore, at that location, much less erosion occurred since 1.8 Ma than in the bottom of the valley. The present elevation of TEKI-23 is ~2100 m above sea level and ~1900 m above sample 01MR-59. The difference in elevation between TEKI-23 and 01MR-59 is in excellent agreement with the minimum amount of erosion inferred solely from 01MR-59. Intense glacial erosion ~1.8 Ma greatly deepened the Klinaklini valley and enhanced topographic relief between the locations of these two samples, although the region's relief before 1.8 Ma cannot be quantified solely from this data set. Further, because TEKI-38 is located at lower elevation than 01MR-59 yet was at lower temperatures, the comparative ^{4}He/^{3}He thermochronometry of these samples implies that glacial valley widening progressed toward the east.

Our results indicate acceleration in rock cooling and erosion rates at a time when widespread glaciation was active in North America, but nearly 900,000 years after the onset of Northern Hemisphere glaciation (*25*). We find that between 1.8 and 1.4 Ma, glacial erosion rates in the Klinaklini valley were significantly higher (by a factor of ≥6) than erosion rates before 1.8 Ma (between ~5 and 1.8 Ma), which more likely involved fluvial processes. The coincidence of this event with other erosion and climate events occurring in both the Northern and Southern hemispheres between 1.9 and 1.7 Ma (*26*–*28*, *32*, *33*) suggests that the intense erosion may be related to a global transition to increased climate variability at that time (*26*, *33*, *34*). This supports the notion that transitions out of periods of climate stability to high-frequency changes in temperature and precipitation enhance erosion by preventing fluvial and glacial systems from establishing new equilibrium states (*34*).

Although glacier ice likely existed within major valleys during more recent glaciations (i.e., after 1.4 Ma), ^{4}He/^{3}He thermochronometry indicates that most of the present relief of the Klinaklini valley developed shortly after continental ice sheets did, and that recent glacial advances resulted in considerably less net erosion within preexisting valleys. Thermochronometric evidence from the northern Coast Mountains revealed an average erosion rate of only 0.22 mm/year between 10 and 4 Ma and suggested a substantial increase in exhumation rate sometime after 4 Ma (*9*). If representative of the entire range, the Klinaklini data set suggests that the Coast Mountains experienced a major topographic modification after 2 Ma.

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17. Separated populations (~mg) of apatites were irradiated with a 220-MeV proton beam generated by isochronous cyclotron acceleration. A fluence of ~10^{15} protons/cm^2 induced a uniformly distributed (*16*) ^{3}He concentration of ~10^8 atoms/mg. After irradiation, the dimensions of ≤20 whole, euhedral, similarly sized, inclusion-free crystals were measured, and the grains were loaded onto a thermocouple in copper foil under vacuum (*35*). Each sample was sequentially heated to a set temperature to ±2°C for a prescribed time [typically a few hours (*24*)], as previously described (*16*, *35*, *36*). After each heating step, the evolved ^{3}He abundance and ^{4}He/^{3}He ratio were measured by sector field mass spectrometry with mass resolution sufficient to resolve ^{3}He from HD. A correction for blank and proton-induced ^{4}He (proton-induced ^{4}He/^{3}He ~ 10) was applied to each measurement. Single grain (U-Th)/He ages were determined on nonirradiated samples by using conventional techniques (*15*). Uncertainties on (U-Th)/He ages were estimated from the reproducibility of replicated analyses, and uncertainties on ^{4}He/^{3}He were dominated by and estimated from uncertainty in ^{4}He blank corrections.
18. Additional details of ^{4}He/^{3}He thermochronometry and complete data sets are available as supporting material on *Science* Online.
19. For instance, a sample that experienced slow cooling will have a diffusive ^{4}He distribution with low concentration near the grain's edge, resulting in gradually increasing ^{4}He/^{3}He ratios upon sequential degassing (*13*). Unlike conventional age-elevation relationships (*37*), the technique does not rely on the relative positions and cooling ages of other samples; each sample provides independent information on its cooling history. By combining the cooling paths of multiple samples (e.g., along a vertical or horizontal transect), the evolving three-dimensional thermal field at depth is revealed. For instance, major changes in the thermal field, e.g., associated with deep glacial incision, should be recorded in proximate samples.
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39. We thank G. Woodsworth for assistance in sample collection and providing access to the Digital Elevation Model used in Fig. 1 through collaboration with the Geologic Survey of Canada. We also thank J. M. Sisterson for help with the proton irradiation, L. M. Hedges for help with sample preparation, and M. S. Densmore. This work was supported by NSF grants EAR-0408526 and 0309779.

Supporting Online Material

www.sciencemag.org/cgi/content/full/310/5754/1668/DC1
SOM Text
Figs. S1 to S5
Tables S1 to S5
References and Notes

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Hf-W Chronometry of Lunar Metals and the Age and Early Differentiation of the Moon

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The use of hafnium-tungsten chronometry to date the Moon is hampered by cosmogenic tungsten-182 production mainly by neutron capture of tantalum-181 at the lunar surface. We report tungsten isotope data for lunar metals, which contain no ^{181}Ta-derived cosmogenic ^{182}W. The data reveal differences in indigenous ^{182}W/^{184}W of lunar mantle reservoirs, indicating crystallization of the lunar magma ocean 4.527 ± 0.010 billion years ago. This age is consistent with the giant impact hypothesis and defines the completion of the major stage of Earth's accretion.

The most widely accepted model for the formation of the Moon involves a catastrophic collision between a Mars-sized body and the proto-Earth. This giant impact most likely occurred during the final stages of accretion and contributed roughly the last 10% of Earth's mass (*1*). As such, the age of the Moon provides the best time marker for the completion of Earth's accretion. Long-lived chronometers have been used to date ancient lunar rocks to 4.56×10^9 to 4.29×10^9 years ago (Ga) (*2*–*4*), but the Moon's exact age has been uncertain.

Hafnium-182 decays to ^{182}W with a half-life of 8.9×10^6 years (My) and is well suited to constrain the time of the Moon's formation (*5*–*7*). However, enhanced ^{182}W/^{184}W in lunar samples (*5*) largely reflect cosmogenic ^{182}W added from neutron capture of ^{181}Ta during the intense cosmic ray exposure of the lunar surface (*8*, *9*). The large corrections introduce uncertainties that exceed the anticipated ^{182}W/^{184}W variations produced in the lunar interior, compromising a reliable interpretation in terms of ^{182}Hf-^{182}W chronometry. Almost all lunar samples contain small amounts of metal, which is enriched in W and contains no detectable Ta (*10*) [Supporting Online Material (SOM) Text 1]. Hence, lunar metals should not carry a cosmogenic ^{181}Ta-derived component. Here, we analyzed these metals to date the formation of the Moon and the crystallization of the lunar magma ocean (LMO) thought to be formed by the giant impact.

Obtaining a Hf-W chronology requires significant variation in Hf/W among the rocks produced in the LMO. The first rocks to crystallize from the LMO consisted mainly of olivine and pyroxene. These were followed by plagioclase-rich cumulates (ferroan anorthosites) that floated to the surface, forming the earliest lunar crust (*11*). The end of the crystallization sequence involved the precipitation of ilmenite and clinopyroxene until solidification of the last few percents of the magma ocean (*11*, *12*). The characteristic features of this residual liquid [termed KREEP for high contents of potassium (K), rare earth elements (REE), and phosphorus (P)] are its strong enrichment in incompatible elements and its uniform elemental and isotopic composition, resulting from global-scale lunar differentiation (*12*, *13*). Subsequent melting and mixing among these primary rocks produced the variety observed in the lunar sample suite (*11*). For example, mare basalts formed by remelting of early mafic cumulates, which in the case of high-Ti mare basalts included assimilation of ilmenite-clinopyroxene. The redistribution of KREEP during impacts on the lunar surface resulted in the contamination of most highland breccias with KREEP, making KREEP the major carrier of incompatible elements in lunar highland rocks. Hf-W fractionations in the crystallizing LMO result from the high incompatibility of W and the compatibility of Hf in clinopyroxene-ilmenite, leading to low Hf/W in KREEP and complementary high Hf/W in the high-Ti mare basalt source (*6*, *7*, *14*). If these Hf-W fractionations occurred during the effective lifetime of ^{182}Hf, variations in the ^{182}W/^{184}W of lunar mantle reservoirs will result.

Table 1. W isotope data and Ta/W and Hf/W for lunar metals and whole rocks. $\varepsilon_W = \{[(^{182}W/^{184}W)_{meas} - (^{182}W/^{184}W)_{std}]/(^{182}W/^{184}W)_{std}\} \times 10^{-4}$. W, Hf, and Ta concentration data are given in table S1. Techniques for the separation of metals and analytical methods for W isotope measurements are described elsewhere (*28*, *29*). All measurements were performed with the IsoProbe (GV Instruments, Manchester, UK) multiconductor inductively coupled plasma mass spectrometer (MC-ICPMS) (*28*) at Universität Münster except those labeled with an asterisk. $\Delta\varepsilon_{W,GCR}$ is the shift in ε_W caused by the interaction with galactic cosmic rays (GCR) and is calculated only for metals by using corrections equations (*15*) and published exposure ages (reference listed in table S2). Details about these correction calculations are given in SOM Text. Corrected ε_W values are obtained as $\varepsilon_{W,corr} = \varepsilon_{W,meas} - \Delta\varepsilon_{W,GCR}$. Repl., replicate.

Sample	Exposure age (Ma)	$\varepsilon_{W,meas} \pm 2\sigma$	$\Delta\varepsilon_{W,GCR} \pm 2\sigma$	$\varepsilon_{W,corr} \pm 2\sigma$
		KREEP-rich samples		
14310 metal	300	–0.10 ± 0.50	–0.26 ± 0.13	0.16 ± 0.52
15445 metal	220	–0.54 ± 0.50		
Repl.	″	0.24 ± 0.50		
Repl.*	″	0.09 ± 0.50		
Mean	″	–0.07 ± 0.29	–0.19 ± 0.10	0.12 ± 0.30
62235 metal	163	–0.39 ± 0.50		
Repl.*	″	0.00 ± 0.50		
Repl.*	″	–0.12 ± 0.50		
Mean	″	–0.17 ± 0.29	–0.14 ± 0.07	–0.03 ± 0.30
62235 whole rock	″	0.80 ± 0.50		
65015 metal	490	–0.54 ± 0.50		
Repl.	″	–0.99 ± 0.50		
Repl.*	″	–1.01 ± 0.50		
Mean	″	–0.85 ± 0.29	–0.43 ± 0.22	–0.42 ± 0.36
65015 whole rock	″	2.40 ± 0.50		
78155 metal	30	–0.39 ± 0.80		
		Low-Ti mare basalts		
15475 metal	529	0.70 ± 0.96	–0.46 ± 0.23	1.16 ± 0.99
15475 whole rock	″	1.00 ± 0.50		
15555 whole rock	80	0.50 ± 0.80		
		High-Ti mare basalts		
72155 metal		1.74 ± 0.72		
72155 whole rock		1.40 ± 1.20		
79155 metal	575	2.31 ± 0.90	–0.51 ± 0.26	2.82 ± 0.94
79155 whole rock	″	37.90 ± 0.80		

*Measurement performed with the Nu Plasma (Nu Instruments, Wrexham, UK) MC-ICPMS at ETH Zürich (*9*).

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We measured the W isotopic composition of eight lunar metals and six whole-rock samples (Table 1). The lunar metals have ε_W values (ε_W defined in Table 1) below or similar to the values obtained for their host rocks (Table 1 and Fig. 1). These differences are most pronounced for samples having old exposure ages and high Ta/W (samples 79155 and 65015) and are lower for samples with lower Ta/W and/or younger exposure ages (Fig. 1B and Table 1). These results corroborate suggestions that enhanced $^{182}W/^{184}W$ in lunar whole-rock samples largely reflect cosmogenic ^{182}W additions via neutron capture of ^{181}Ta (*8*, *9*).

The $^{182}W/^{184}W$ of lunar metals could have been slightly lowered by neutron capture of W isotopes during cosmic ray exposure at the lunar surface. In contrast to the substantial ^{182}W production by neutron capture of ^{181}Ta, the effects of ^{182}W burnout are small (*8*, *15*) and require only corrections that in most cases are smaller than the uncertainty of the W isotope measurements. Exposure ages for the KREEP-rich samples we examined range from ~160 to ~500 My, but the metals of these samples have similar ε_W values, providing further evidence that the effects of ^{182}W burnout are small. Sample 65015 has the longest exposure time and appears to have a slightly, albeit barely resolvable, lower ε_W compared to the other KREEP metals. This difference disappears after the effects of ^{182}W burnout are taken into account (Table 1, Fig. 2, and SOM Text 2). The lower exposure ages for samples 14310, 15445, and 62235 require corrections that are smaller than the analytical uncertainty of the W isotope measurements, indicating that the W isotope composition of KREEP can reliably be deduced from these samples, yielding an average ε_W of 0.06 ± 0.20 (2σ).

Low-Ti mare basalt 15555 shows no resolvable cosmogenic ^{182}W effects (*9*), and its average ε_W is 1.18 ± 0.20 [this study and (*9*)], identical to the corrected value for the metal of sample 15475 (Fig. 2). The exposure time of high-Ti mare basalt 72155 is unknown, but the similarity in the metal and whole-rock data in conjunction with a high Ta/W of ~20 in the bulk sample suggest only minor cosmic ray–induced shifts in the metal and bulk rock. This is consistent with the fact that the measured ε_W of the 72155 metal is indistinguishable from the corrected ε_W of the 79155 metal. High-Ti mare basalts thus have an indigenous W isotope composition (weighted mean ε_W = 2.14 ± 0.57) that is slightly more radiogenic than that of low-Ti mare basalts (ε_W = 1.18 ± 0.20) and significantly more radiogenic than that of KREEP (ε_W = 0.06 ± 0.20) (Fig. 2).

The $^{182}W/^{184}W$ variations require the existence of at least three major lunar mantle reservoirs that acquired their distinct Hf/W ratios during the effective lifetime of ^{182}Hf. Determination of Hf-W ages requires knowledge of the Hf/W ratios in the source areas prevailing during ^{182}Hf decay. Measured Hf/W ratios of lunar samples are the complex product of multiple melting events and do not provide a firm measure of the Hf/W ratio in the sources. Age information can be obtained by assuming the maximum range of Hf/W that can have been generated in the source areas. The uncertainties inherent in these estimates have little effect on the robustness of the calculated ages, because these are largely constrained by the well-resolved ε_W differences.

The range in ε_W values that could have been produced in the lunar mantle is illustrated in Fig. 3A. The $^{182}W/^{184}W$ variations are expressed as the deviation from the bulk LMO as represented by the $^{182}W/^{184}W$ ratio of low-Ti mare basalts. Their source region consists of olivine and orthopyroxene cumulates, the crystallization of which did not involve any substantial Hf-W fractionation (*14*). This is consistent with the absence of ^{142}Nd anomalies (from the decay of ^{146}Sm) in these rocks (*16*). Palme and Rammensee (*17*) estimated U/W = 1.93 for the lunar mantle, corresponding to Hf/W = 26.5. This Hf/W ratio is similar to measured values for low-Ti mare basalts (table S1) (*5*), consistent with limited Hf-W fractionation during melting of olivine-orthopyroxene cumulates (*14*).

The relatively low ε_W of KREEP requires that its source evolved with a Hf/W ratio below that of the low-Ti mare basalt source, consistent with Hf/W ~ 12 to 19 for the KREEP source (*12*, *13*). Measured Hf/W ratios of ~20 for KREEP-rich samples provide an upper limit to the Hf/W ratio because KREEP constitutes the reservoir with the lowest Hf/W ratio in the lunar mantle; contamination of KREEP with other mantle sources can only have increased the Hf/W ratio. The redistribution of KREEP during impacts on the lunar surface involved no Hf-W fractionation, as indicated by the uniform chemical composition of KREEP. Given the higher in-

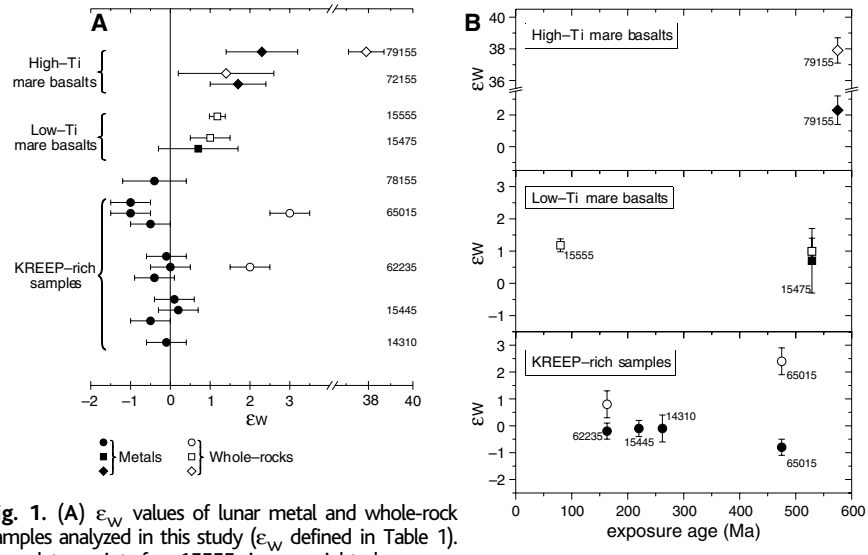

Fig. 1. (**A**) ε_W values of lunar metal and whole-rock samples analyzed in this study (ε_W defined in Table 1). The data point for 15555 is a weighted average calculated from the combined data from this study and Lee *et al*. (*9*). (**B**) ε_W versus exposure age for lunar metals and whole-rock samples. Exposure ages are from the literature (table S2). The ε_W values for whole-rock samples depend on both Ta/W (Table 1) and exposure age. In contrast, metals contain no Ta and hence no cosmogenic ^{182}W. Error bars indicate 2σ.

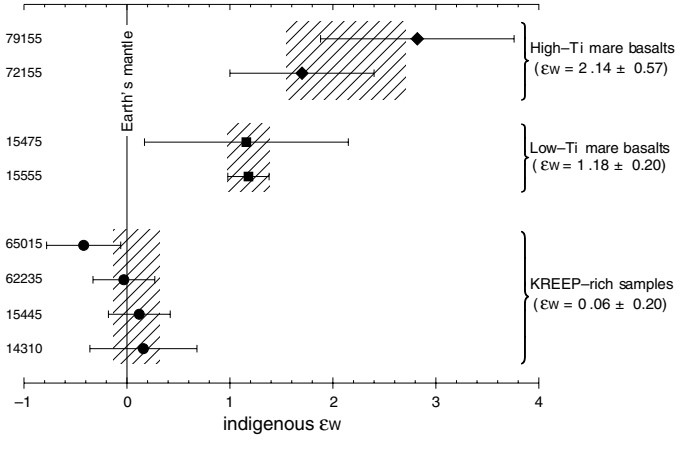

Fig. 2. Indigenous ε_W of lunar mantle reservoirs. Plotted are the corrected ε_W values for metals (Table 1). Samples 15555 and 72155 show only negligible cosmic ray effects, such that the data require no correction. Earth's mantle (ε_W = 0) is shown for comparison. Error bars indicate 2σ.

compatibility of W relative to Hf, partial melting in the high-Ti mare basalt source should result in a lower Hf/W ratio in the melt compared with the residue, implying that the source Hf/W ratio should be higher than that measured for high-Ti mare basalts (up to ~110). These basalts, however, formed several hundreds of millions of years after the primary differentiation of the Moon, such that their Hf/W ratio will reflect the increasing degree of source depletion by multiple melt extractions. On the basis of Hf and W partition coefficients, Righter and Shearer (*14*) calculated Hf/W > 40 for the high-Ti mare basalt source, implying a lower Hf/W ratio in the original reservoir than in high-Ti mare basalts themselves, consistent with their only slightly enhanced $^{182}W/^{184}W$ ratio.

Regardless of any uncertainties inherent in the estimated source Hf/W ratio, the latest possible time of differentiation can be obtained by assuming Hf/W = 0 for the reservoir with the lowest ε_W (i.e., the KREEP source). This age constraint is independent of any uncertainties in the Hf/W ratio of the KREEP source. If Hf/W = 0, the $^{182}W/^{184}W$ difference between KREEP and low-Ti mare basalts must have been generated no later than ~50 My after formation of calcium-aluminum-rich inclusions (CAIs) (Fig. 3). This is the latest possible time for differentiation because KREEP likely has Hf/W > 0, in which case less time is required to generate the ε_W difference between the KREEP and low-Ti mare basalt sources (Fig. 3). This age constraint is not very sensitive to uncertainties in the estimated Hf/W ratio of the bulk LMO, because a 50% variation in the Hf/W ratio of the bulk LMO (i.e., from 20 to 33) would result in an uncertainty of only ±3 My in the above age estimate. The latest possible time for differentiation in the high-Ti mare basalt source is less well constrained (mainly reflecting uncertainties in the upper limit of the source Hf/W) but is consistent with the ~50-My age estimate derived for KREEP (Fig. 3).

The earliest possible time of lunar differentiation is less well constrained because it must rely on independent estimates of Hf/W ratios in the different reservoirs. However, both the upper limit of Hf/W < 20 in the KREEP source and the lower limit of Hf/W > 40 in the high-Ti mare basalt source constrain the earliest possible time of differentiation to ~30 My (Fig. 3). This is consistent with ~30-My W model ages for the Moon (*18*–*20*), which some authors (*21*, *22*) interpret as the earliest possible time the Moon could have formed. This suggests that the upper and lower limits for the KREEP and high-Ti mare basalt sources, respectively, are reasonable.

The preservation of W isotopic variations indicates that there was negligible mixing in the lunar interior since its earliest differentiation, because any W isotopic variability would have been effectively erased by convective overturn in a largely molten magma ocean. Thus, the LMO must have formed and crystallized from 30 to 50 My after the start of the solar system, i.e., 4.537 to 4.517 Ga. Three observations suggest that the observed ε_W variations directly result from Hf-W fractionation in the final stages of LMO crystallization. First, the W isotopic variations correlate with Hf/W ratios anticipated for fractionation in a crystallizing LMO (Fig. 3B). Second, KREEP is strongly enriched in W, such that resetting the W isotopic composition of KREEP would require substantial isotopic exchange between KREEP and the other reservoirs of the lunar mantle. It is thus more likely that KREEP preserved the W isotope composition acquired at the final stage of LMO crystallization. Third, mixing of late-stage ilmenite-clinopyroxene cumulates with olivine as a result of cumulate overturn (*23*) would only shift the data point for the high-Ti mare basalt source downward to lower Hf/W ratios and ε_W values along the reference isochron (Fig. 3B). However, even if the $^{182}W/^{184}W$ variations did reflect post-LMO events, the Hf-W age would still provide the latest possible time for the crystallization of the LMO.

Rapid crystallization of the LMO 30 to 50 My after solar system formation contrasts with models that involve a long-lived (100 to 200 My) magma ocean (*24*), implying that the earliest lunar crust was not insulating enough to prevent rapid heat loss (*7*, *14*). The ferroan anorthosites are regarded as remnants of the earliest lunar crust and if so must have formed before complete solidification of the magma ocean more than before 4.517 Ga. ^{147}Sm-^{143}Nd ages for some ferroan anorthosites [e.g., 4.44 ± 0.02 Ga for 60025 (*2*) and 4.29 ± 0.06 Ga for 62236 (*4*)], however, are younger, indicating that they do not date primary crust formation. Likewise, the ^{146}Sm-^{142}Nd model age of the lunar mantle [~4.32 Ga (*16*)] as well as Rb-Sr [4.42 ± 0.07 Ga (*25*)] and ^{147}Sm-^{143}Nd [4.36 ± 0.06 Ga (*26*)] model ages for KREEP are younger than the Hf-W age of >4.517 Ga. These younger ages must reflect post-LMO events such as remelting, mixing, and impact metamorphism. The latter might have aided to destabilize the earliest lunar crust, which is required for rapid cooling of the LMO (*7*).

The giant Moon-forming impact is the last major event in Earth's accretion (*1*), such that the date of this event should define the age of both the Earth and Moon. ^{182}Hf-^{182}W model ages for the Earth and Moon strongly depend

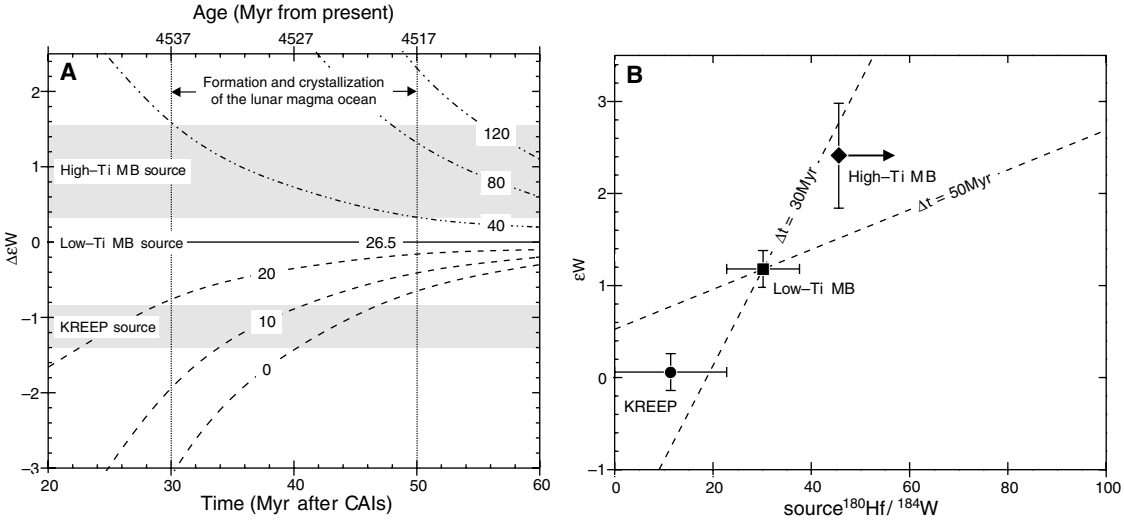

Fig. 3. (**A**) ε_W variations in the lunar mantle depending on Hf/W and time. Hf/W ratios between 0 and 120 cover the range of measured Hf/W ratios in lunar samples and estimated Hf/W ratios in the crystallizing LMO. $\Delta\varepsilon_W$ is the deviation of ε_W from the bulk LMO [ε_W = 1.18 ± 0.20, Hf/W = 26.5]. The numbers on curves indicate Hf/W ratios of the modeled reservoirs. The gray shaded areas indicate the ε_W deviation (expressed in $\Delta\varepsilon_W$) of the KREEP and high-Ti mare basalt sources from the low-Ti mare basalt source. Time of differentiation is calculated relative to $^{182}Hf/^{180}Hf = 1.07 \times 10^{-4} \pm 0.10 \times 10^{-4}$ for CAIs (*27*). (**B**) ε_W versus $^{180}Hf/^{184}W$ in the sources. Reference isochrons corresponding to differentiation at 30 and 50 My after CAI formation are shown. Assumed Hf/W ratios are 10 ± 10 for KREEP, 26.5 ± 6.5 for the low-Ti mare basalt source, and >40 for the high-Ti mare basalt source. Error bars indicate 2σ.

on the model applied (particularly on the assumed degree of metal-silicate equilibration during core formation), resulting in age estimates ranging from ~30 to >100 My after solar system formation (*20*–*22*). In contrast, the Hf-W age of LMO crystallization tightly constrains the age of the Moon and the final stage of Earth's accretion to 30 to 50 My after the formation of the solar system. The formation of the Moon significantly later than that of asteroids and Mars (*18*, *27*) underpins the Moon's origin by a unique event, as required in the giant impact hypothesis.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/310/5754/1671/DC1
SOM Text
Tables S1 and S2
References

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The Importance of Land-Cover Change in Simulating Future Climates

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Adding the effects of changes in land cover to the A2 and B1 transient climate simulations described in the Special Report on Emissions Scenarios (SRES) by the Intergovernmental Panel on Climate Change leads to significantly different regional climates in 2100 as compared with climates resulting from atmospheric SRES forcings alone. Agricultural expansion in the A2 scenario results in significant additional warming over the Amazon and cooling of the upper air column and nearby oceans. These and other influences on the Hadley and monsoon circulations affect extratropical climates. Agricultural expansion in the mid-latitudes produces cooling and decreases in the mean daily temperature range over many areas. The A2 scenario results in more significant change, often of opposite sign, than does the B1 scenario.

As anthropogenic impacts on Earth's surface continue to accelerate, the effects of these actions on future climate are still far from known (*1*–*3*). Historical land-cover conversion by humans may have decreased temperatures by 1° to 2°C in mid-latitude agricultural regions (*4*–*9*). Simulations of tropical deforestation (*10*–*12*) and potential future human land-cover impacts project a warming of 1° to 2°C in deforested areas (*13*, *14*), with possible extratropical impacts due to teleconnection processes (*7*, *11*, *13*, *15*). However, most of these experiments have been performed in uncoupled or intermediate-complexity climate models and have not followed the proposed framework of the Intergovernmental Panel on Climate Change (IPCC) Special Report on Emissions Scenarios (SRES) (*16*). The study described here evaluated whether future land use decisions, based on assumptions similar to those used to create the IPCC SRES atmospheric forcing scenarios, could alter the outcomes of two future IPCC SRES climate simulations.

Land-cover impacts on global climate can be divided into two major categories: biogeochemical and biogeophysical (*2*, *14*–*18*). Biogeochemical processes affect climate by altering the rate of biogeochemical cycles, thereby changing the chemical composition of the atmosphere. To some extent, these emissions are included in the IPCC climate change assessments (*1*). Biogeophysical processes directly affect the physical parameters that determine the absorption and disposition of energy at Earth's surface. Albedo, or the reflective properties of Earth's surface, alters the absorption rate of solar radiation and hence energy availability at Earth's surface (*4*–*19*). Surface hydrology and vegetation transpiration characteristics affect how energy received by the surface is partitioned into latent and sensible heat fluxes (*4*–*19*). Vegetation structure affects surface roughness, thereby altering momentum and heat transport (*12*). Summarizing the effects of land-cover change on climate has been difficult because different biogeophysical effects offset each other in terms of climate impacts (*16*), and, on global and annual scales, regional impacts are often of opposite sign and are therefore not well represented in annual global average statistics (*7*, *16*).

For this study, we used the fully coupled Department of Energy Parallel Climate Model (DOE-PCM) (*20*, *21*) to simulate combined land-cover and atmospheric forcings for the A2 and B1 IPCC SRES scenarios (*22*). Atmospheric forcings were identical to those used in previous IPCC SRES scenario experiments, resulting in a 1°C warming for the low-impact B1 scenario and a 2°C warming for the high-impact A2 scenario (*20*). To simulate future land-cover change, we used the Integrated Model to Assess the Global Environment (IMAGE) 2.2 IPCC SRES land-cover projections (*7*, *22*–*24*) and DOE-PCM natural vegetation data to create land-cover data sets

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representing SRES B1 and A2 scenarios for the years 2050 and 2100 (Fig. 1) [for further details, see section A of the Supporting Online Material (*25*)]. For each SRES scenario, we ran the model from 2000 to 2033 with present-day land cover, from 2033 to 2066 with 2050 land cover, and from 2066 to 2100 with 2100 land cover. The model ran in transient mode, using IPCC atmospheric forcings from 2000 to 2100 (*20*). For comparison, we ran the same simulations with identical IPCC SRES atmospheric forcing while holding land cover constant at the present-day conditions (Fig. 1). To isolate the effects produced by land-cover change, results are presented as the difference between the all-forcing scenario (atmospheric and land-cover) and the atmospheric forcing with constant land cover. To illustrate the robustness of our results, we conducted a second A2 scenario simulation that held land cover constant at present conditions to 2066 and then switched to the A2 2100 land-cover scenario [for further details, see section B of the Supporting Online Material (*25*)]. This experiment showed almost identical results, with similar statistical significance, as the initial A2 2100 experiment (fig. S1).

Land-cover change effects on global surface temperatures differ significantly between the A2 and B1 climate scenarios (Fig. 2). However, globally averaged annual temperature differences for a given scenario are less than 0.1°C for all the simulations because of offsetting regional climate signals. Most significant regional climate effects are associated directly with land-cover conversions in mid-latitude and tropical areas. At higher latitudes, temperature responses are not directly linked to local land-cover change and can change sign by season (Fig. 2). Compared to surface temperature responses, land-cover change has a more significant effect on diurnal temperature ranges (DTRs) (Fig. 3). All scenarios show widespread DTR responses to land-cover change, and many of the changes correspond directly with areas of land-cover change. In three of the four scenarios, the DTR decreases significantly in southern Asia; and in the A2 scenarios, significant portions of the mid-latitude land areas experience decreases in DTRs. To better understand the potential effects and mechanisms of the impacts of land-cover change, six regions have been selected to illustrate the nature of the response (Fig. 1).

In the Amazon, the direct effect of converting tropical broadleaf forest to agriculture in the A2 2100 scenario is a significant warm-

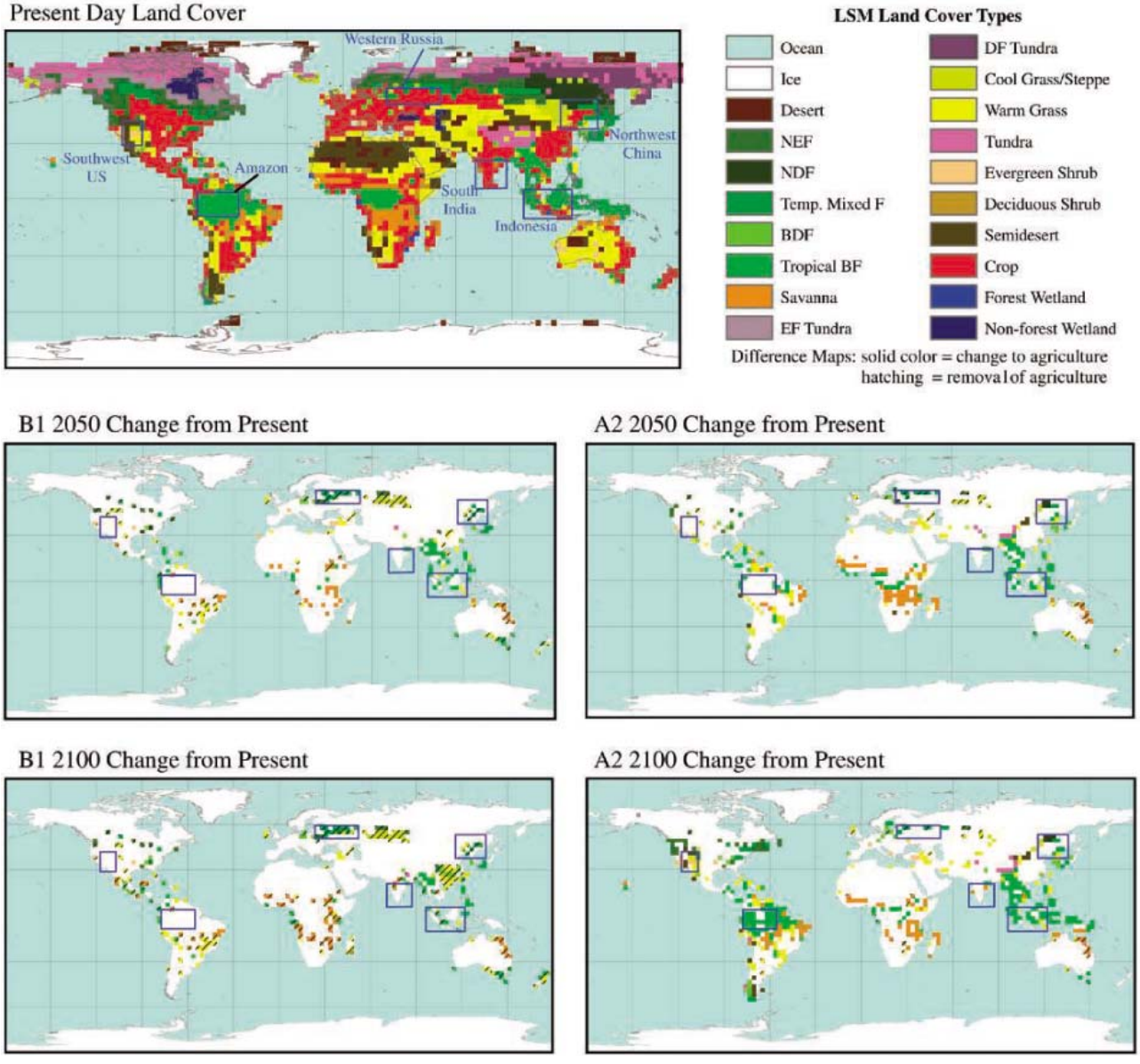

Fig. 1. Representation of present-day land cover and land-cover change for each of the scenarios. Each of the six tropical regions discussed in the text is indicated. B, broadleaf; N, needleleaf; E, evergreen; D, deciduous; and F, forest.

ing, well above 2°C (Fig. 2). However, the same land-cover conversion results in relatively minor temperature responses in Indonesia. From these observations, it is apparent that tropical locations with the same land-cover forcing have different responses, as has been shown in other studies (*12*, *13*). To assess these different regional responses, we evaluated temperature responses in all grid cells that were converted from tropical broadleaf evergreen forest to agriculture [for further details, see section C of the Supporting Online Material (*25*)]. In almost all cases, this land-cover change has minor effects on daily maximum temperatures. However, in the Amazon there is a significant increase in daily minimum temperatures, an effect not observed in Indonesia (fig. S2). The changes in minimum temperatures are most often associated with dry periods [for further details, see section C of the Supporting Online Material (*25*)]. Therefore, it is primarily the increase in daily minimum temperatures, typically at nighttime, that affects the DTR in tropical regions. Increased nighttime temperatures are known to cause a disproportionate human stress response (*26*).

Further analysis of the tropical regions shows that in the Amazon, net radiation changes in the atmospheric forcing scenarios are primarily offset by increases in latent heat fluxes when tropical forests are present. These increases in latent heat fluxes increase cloud cover and minimize temperature impacts. In comparable land-cover and atmospheric forcing simulations, the lower leaf-area index over the region reduces latent heat flux and cloud cover, resulting in increased incident radiation. These processes increase surface temperatures and sensible heat flux. In the present-day and A2 atmospheric forcing scenarios, moisture fluxes from canopy evaporation, ground evaporation, and transpiration are partitioned as 22, 20, and 58%, respectively. When the A2 2100 land-cover change is included, this changes to 10, 63, and 26%. In contrast, In-

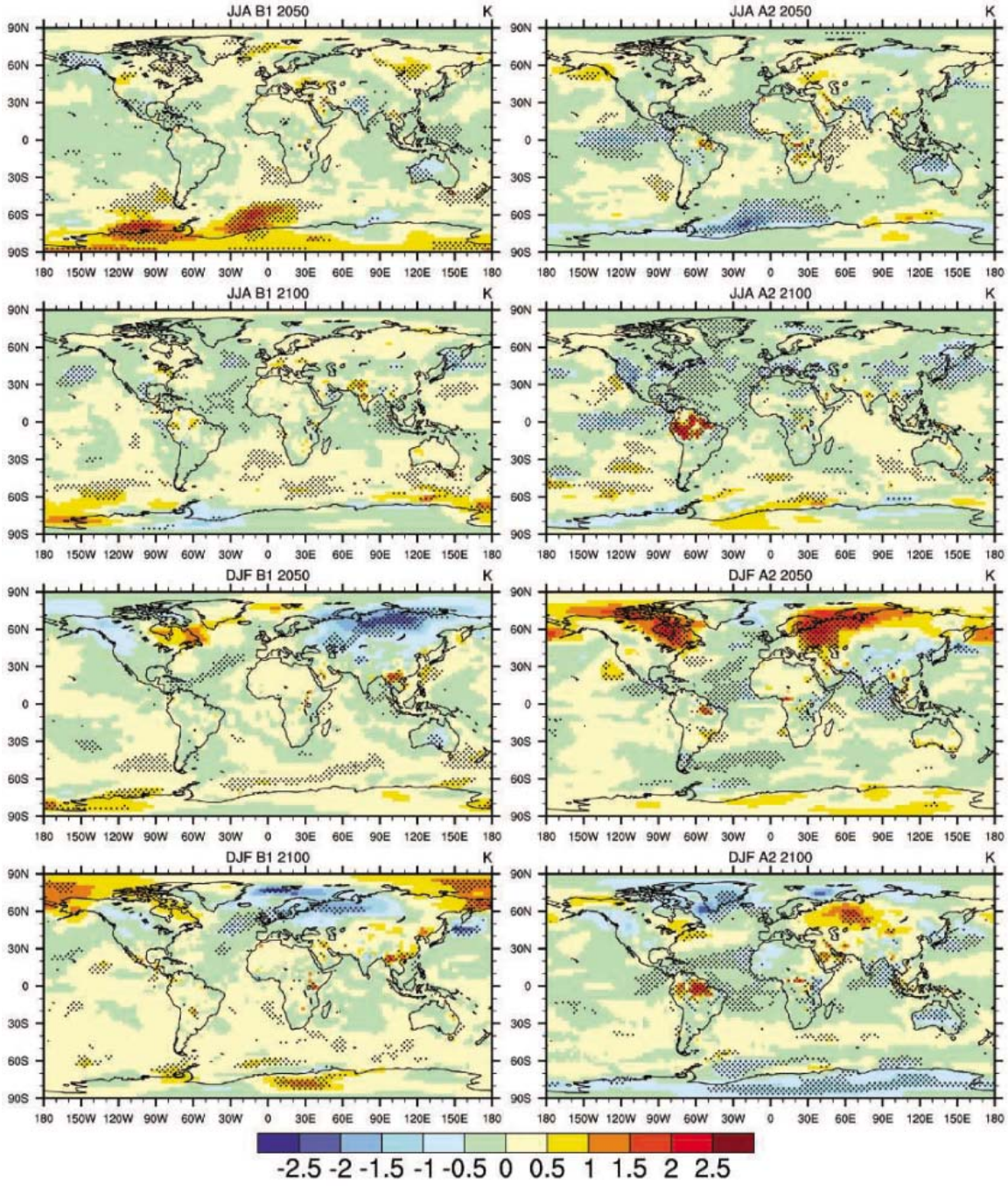

Fig. 2. JJA and DJF temperature differences due to land-cover change in each of the scenarios. Values were calculated by subtracting the greenhouse gas–only forcing scenarios from a simulation including land-cover and greenhouse gas forcings. Shaded grid cells are significant at the 0.05 confidence level. The top four panels show JJA; the bottom four show DJF. B1 scenario results are on the left and A2 results are on the right.

donesia does not experience a reduction in latent heat flux even though there is a 20% reduction in the fraction of latent heat flux that is transpired. In this case, an increase in local rainfall provides water to increase evaporation rates, thereby compensating for increases in sensible heat flux and temperature. The lack of response over Indonesia can be attributed to the effects of the Asian Monsoon circulation and precipitation regime, which override feedbacks from local land-cover change.

Although the Asian Monsoon suppresses the Indonesian response to land-cover forcing, other large-scale land-cover forcings in East Africa, Australia, and southern and eastern Asia appear to affect the strength and timing of the large-scale Asian Monsoon circulation. This results in climate impacts over a number of areas that are influenced by the Asian Monsoon. For example, both 2050 scenarios over India in June, July, and August (JJA) show increased cloud cover and precipitation, resulting in decreased incident radiation and higher latent heat fluxes. This effect occurs despite local reductions in transpiration efficiencies due to local land-cover change. This reverses in the A2 2100 scenario, perhaps because the effect of African land-cover change on the monsoon circulation is reduced. The B1 2100 scenario, with global reforestation, results in significantly dryer and warmer Indian climates. Similar impacts occur in East Africa and northern Australia. Temperatures over the Indian Ocean are also affected, with possible consequences for the North Atlantic Oscillation (*27*).

Compared to Asia, Amazonian land-cover feedbacks have much greater local impacts. Although surface temperatures increase dramatically in response to land-cover forcing, temperatures in the air column above show a significant cooling as compared to the atmospheric forcing scenario. This slows the regional Hadley circulation and has significant impacts over nearby ocean areas. The Atlantic Ocean experiences a significant cooling that extends from the tropical warm pool to much of the North Atlantic in the A2 2100 JJA scenario. The eastern equatorial Pacific also shows a significant cooling response in the A2 scenario, suggesting more La Niña–like conditions. In the B1 scenario, a slight cooling in the western equatorial Pacific Ocean in 2050 and slight warming over the eastern Pacific Ocean in 2100 suggest a more El Niño–like state.

The impacts of land-cover change on extratropical climates are in response to a mixture of local land-cover change effects and changes in the large-scale circulation system. The conversion of mid-latitude forests and grasslands to agriculture is generally thought to cool mean daily maximum temperatures (*28*, *29*). This direct land-cover effect is evident in northeast China, where the conversion to agriculture results in relative cooling (or reduced warming in the all-forcing scenario) and decreased DTR due to increases in winter albedo and summer evapotranspiration efficiencies. This contrasts strongly with the warming, also in southern China, in the B1 scenario when existing agricultural areas are replaced with forest.

In the A2 2100 scenario, a less direct response to land cover is observed in the southwestern United States. There, transpiration efficiencies increase significantly with local land conversion to agriculture. But increased latent heat fluxes are only realized because of a significant increase in local precipitation, a result that is opposite to that found in similar uncoupled studies (*15*). In this case, the weakened Hadley circulation, caused by Amazon deforestation and cooler temperatures over the neighboring ocean areas, allows a greater northward migration of the Intertropical Convergence Zone (ITCZ) and more moisture entrainment to intensify southwest monsoon precipitation in summer. The increase in latent heat flux, from increased water availability and transpiration efficiency, results in the cooling of mean daily maximum temperatures. The same process also explains the cooling over the eastern Pacific and western Atlantic Oceans, where increased cloud cover and precipitation associated with an expanded northward migration of the ITCZ result in cooler temperatures.

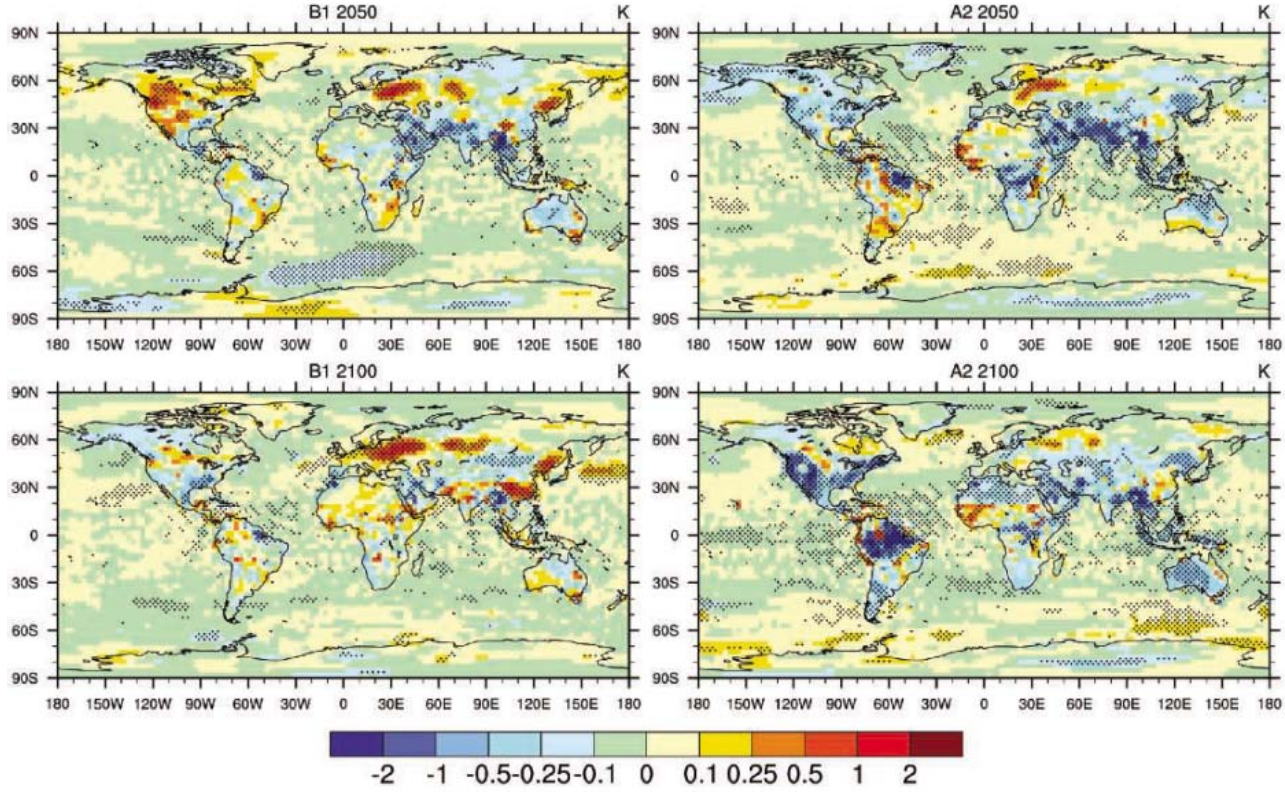

Fig. 3. Changes in the annual average diurnal temperature range due to land-cover change in each of the scenarios. Values were calculated by subtracting the greenhouse gas–only forcing scenarios from a simulation including land-cover and greenhouse gas forcings. Shaded grid cells are significant at the 0.05 confidence level.

In higher-latitude areas, particularly in the Northern Hemisphere, there are significant temperature changes that do not appear to be directly related to land-cover change. Although statistically significant, these changes are relatively small as compared to the projected atmospheric forcing changes. For example, in western Russia there is reforestation in both scenarios, which should lead to warming. However, although the additional land-cover changes have the expected impact on net radiation, the B1 and A2 scenarios show strongly opposing temperature signals in December, January, and February (DJF). These results appear to be closely linked to changes in regional precipitation and may be the result of teleconnections, either linked to the Asian Monsoon circulation or indirect effects from temperature changes over the tropical Pacific and North Atlantic Oceans.

Results from this study suggest that the choices humans make about future land use could have a significant impact on regional and seasonal climates. Some of these effects are the result of direct impacts of land-cover change on local moisture and energy balances. Other impacts appear to be related to significant indirect climate effects through teleconnection processes. The A2 land-cover scenario shows that tropical rainforest conversion will likely lead to a weakening of the Hadley circulation over much of the world and to significant changes in the Asian Monsoon circulation. Especially in the A2 2050 scenario, the interplay between Asian and African land-cover change affects the Asian Monsoon circulation. The Indian Ocean experiences a significant reduction in surface pressure, resulting in increased cloud cover and precipitation and warmer surface temperatures, and these effects extend over most of the Indian subcontinent.

We conclude that the inclusion of land-cover forcing, thereby accounting for a number of additional anthropogenic climate impacts, will improve the quality of regional climate assessments for IPCC SRES scenarios. Although land-cover effects are regional and tend to offset with respect to global average temperatures, they can significantly alter regional climate outcomes associated with global warming. Beyond local impacts, tropical land-cover change can potentially affect extratropical climates and nearby ocean conditions through atmospheric teleconnections. In this respect, our fully coupled experiments differ from previous fixed ocean temperature studies (*12*, *13*, *15*). Further study is needed to determine the exact nature of these responses. Overall, the results demonstrate the importance of including land-cover change in forcing scenarios for future climate change studies.

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Equivalent Effects of Snake PLA2 Neurotoxins and Lysophospholipid–Fatty Acid Mixtures

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Snake presynaptic phospholipase A2 neurotoxins (SPANs) paralyze the neuromuscular junction (NMJ). Upon intoxication, the NMJ enlarges and has a reduced content of synaptic vesicles, and primary neuronal cultures show synaptic swelling with surface exposure of the lumenal domain of the synaptic vesicle protein synaptotagmin I. Concomitantly, these neurotoxins induce exocytosis of neurotransmitters. We found that an equimolar mixture of lysophospholipids and fatty acids closely mimics all of the biological effects of SPANs. These results draw attention to the possible role of local lipid changes in synaptic vesicle release and provide new tools for the study of exocytosis.

SPANs are major protein components of the venom of many snakes (*1*–*3*). They block the NMJ in a characteristic way (*3*–*7*). The phospholipase A2 (PLA2) activity varies greatly among different SPANs, and its involvement in the NMJ block is still debated (*3*, *8*, *9*). There is only a partial correlation between PLA2 activity and neurotoxicity among SPANs and no overlap of surface residues required for neurotoxicity with those essential for PLA2 activity (*8*, *10*). Here, we compared the effects of SPANs on the mouse NMJ hemidiaphragm preparation and on neurons in culture with those of their hydrolysis products: lysophospholipids (LysoPL) and fatty acids (FAs). To conclusive-

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ly determine the nature of SPAN hydrolysis products, cerebellar neurons were treated with SPANs, and their lipid composition was determined by mass spectrometry. The major hydrolytic substrate was phosphatidylcholine, the main phospholipid of the outer leaflet of the plasma membrane (fig. S1). SPAN hydrolysis generated several lysophosphatidylcholines (LysoPC), including myristoyl lysophosphatidylcholine (mLysoPC), and FA. SPANs were not selective for a particular FA species (such as arachidonic acid) and released mainly oleic acid (OA), the most abundant FA of these cells.

The incubation of cerebellar neurons with mLysoPC+OA (30 μM each) led to the incorporation of 6.3 nmol of mLysoPC/10^5 cells, compared with 2.3 nmol/10^5 cells treated with 6 nM taipoxin. mLysoPC+OA did not cause acylation, because the 14.0 to 16.0 ratio in PC did not increase. The values of LysoPC associated with neurons in the two cases were closely comparable, particularly if one considers that SPANs induce a localized release of LysoPL and FA, whereas the incubation with mLysoPC+OA presumably caused generalized lipid insertion.

mLysoPC+OA added to a mouse hemidiaphragm in a physiological medium caused a progressive NMJ paralysis with a time course superimposable to that observed with a typical SPAN (Fig. 1A). Four SPANs of different structural complexity and relative toxicity were used: the single-chain notexin (14 kD, from *Notechis scutatus*), the two-subunit β-bungarotoxin (21 kD, from *Bungarus multicinctus*), the three-subunit taipoxin (42 kD, from *Oxyuranus scutellatus*), and the five-subunit textilotoxin (72 kD, from *Pseudonaja textilis*) (*1*). They induced closely similar paralysis profiles, although with slightly different kinetics; one representative trace is shown. When textilotoxin and mLysoPC+OA were present at the same time (1.5 nM and 50 μM, respectively), a synergistic effect was observed, with the time required to achieve 50% of paralysis ($t_{1/2}$) shorter by a factor of 4 ± 0.5 times (n = 4) than that of textilotoxin. Pancreatic PLA2 (at a concentration matching the activity of textilotoxin in Fig. 1A) did paralyze the NMJ, but with a $t_{1/2}$ three times as long, presumably because of a reduced membrane interaction.

Of the two products of SPAN phospholipid hydrolysis, LysoPC alone was capable of inhibiting the NMJ, although with low potency, whereas FA was poorly effective below the threshold concentration inducing myotoxicity; however, FA and LysoPC clearly acted synergistically (Fig. 1B).

Similar results were obtained with other LysoPL, such as the ethanolamine, serine, and glycerol derivatives. We also tested the effect of LysoPC esterified with FAs of different length and saturation obtaining similar results, but different kinetics, with the following order of $t_{1/2}$: myristoyl-LysoPC (taken as 1, to normalize the data obtained in five different experiments), oleoyl-LysoPC (2.2 ± 0.5 times as long), palmitoyl-LysoPC (3.2 ± 1.3), and stearoyl-LysoPC (8.5 ± 0.6). Their potency correlates with their critical micellar concentrations (*11*, *12*), indicating that the more water-soluble LysoPC equilibrates more rapidly into the membrane and acts faster; it is also possible that the shorter LysoPL causes a higher constraint on the membrane curvature. The paralysis was not due to an effect of mLysoPC+OA on the muscle itself, because direct muscle stimulation elicited full contraction and the muscle maintained its normal ultrastructure (Fig. 1, C and D). The mLysoPC+OA mixture induced diagnostic alterations in the ultrastructure of the NMJ, including a reduction of the number of synaptic vesicles and an enlargement of the nerve terminal (Fig. 1C), which closely mimic the changes observed in SPAN-treated NMJs (*4*–*7*).

SPANs induced a characteristic swelling of synaptic boutons in cultured neurons, with depletion of synaptic vesicles, release of glutamate and FM1-43, and surface exposure of the intralumenal portion of the synaptic vesicle protein synaptotagmin I (SytI) (*13*, *14*). Similarly to SPANs, mLysoPC+OA induced bulges (Fig. 2A) that were strongly stained by an antibody specific for the lumenal domain of SytI in the absence of membrane permeabilization, indicating a persistent surface exposure of the inside of synaptic vesicles (Fig. 2B). Control experiments showed no labeling with an antibody specific for a cytosolic SytI epitope, indicating that the mLysoPC+OA mixture did not permeabilize the neuronal membrane. Bulges were also stained by an antibody specific for synaptophysin I, a marker of synaptic vesicles, showing that they are sites of synaptic vesicle accumulation (fig. S2). Concomitantly to bulge formation, mLysoPC+OA induced neurons to release glutamate as SPANs did (respectively, 92 ± 1% and 78 ± 1% of the amount released upon incubation with 55 mM KCl, taken as 100%; n = 5). Thus, mLysoPC+OA acts at nerve terminals in a manner identical, or superimposable, to that of SPANs.

The biological action of SPANs at nerve terminals can now be rationalized as follows: SPANs bind nerve terminals via receptors whose nature may differ for different SPANs (*1*–*3*), gaining access to membrane phospholipids that are hydrolyzed to LysoPL and FA. LysoPL remain confined mainly to the external leaflet of the presynaptic membrane, whereas FAs have a high rate of transbilayer movement (*15*) and will partition between the two membrane leaflets. Such configuration, with the inverted cone-shaped LysoPL in *trans* and the cone-shaped FA in *cis,* with respect to the membrane fusion site, promotes the fusion-through-hemifusion pathway (*16*, *17*). This would promote neurotransmitter release (*13*, *14*). Hemifusion lipid intermediates have been recently observed in the SNARE-mediated membrane fusion (*18*–*20*). A local change of lipid composition within the site of assembly of the SNARE complex has been suggested to promote the fusion of synaptic vesicles with the presynaptic membrane (*21*–*23*), and there is evidence for the involve-

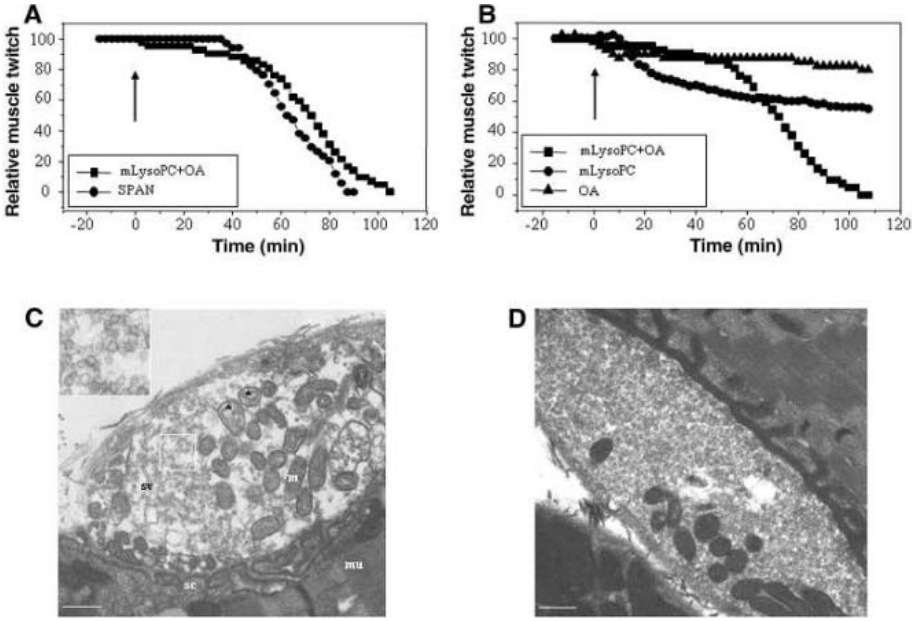

Fig. 1. Paralysis induced by mLysoPC+OA (bath concentration 150 μM) or textilotoxin (15 nM) added (arrows) to the medium of mouse phrenic nerve-hemidiaphragm (**A**). Similar curves were obtained with other SPANs (notexin, β-bungarotoxin, and taipoxin) and other lipid mixtures. (**B**) Activity of the lipid species (150 μM) alone or together. Representative traces are shown in (A) and (B) ($n \geq 5$). (**C**) Representative electron micrographs of a mouse hemidiaphragm paralyzed with mLysoPC+OA (150 μM) and of the corresponding contralateral muscle (**D**). mu, muscle; sc, synaptic cleft; sv, synaptic vesicles. The inset shows an enlarged area containing sv; asterisks indicate swollen mitochondria (m). Scale bar, 0.5 μm.

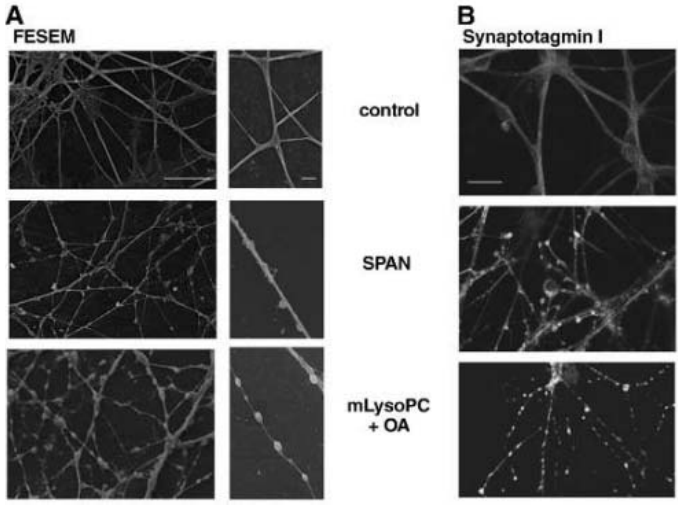

Fig. 2. Field emission scanning electron microscopy (FESEM) of cerebellar granular neurons exposed to taipoxin (6 nM for 60 min) or mLysoPC+OA (30 μM for 15 min) at lower (left panels) and higher (right panels) magnifications (**A**). Identical results were obtained with notexin, β-bungarotoxin, and textilotoxin. Scale bar, 10 μm (left panels) and 2 μm (right panels). (**B**) Cerebellar neurons were exposed to 6 nM β-bungarotoxin for 60 min or to 30 μM mLysoPC+OA for 15 min and stained with an antibody specific for the lumenal domain of synaptotagmin I before fixation. Samples were processed for indirect immunofluorescence without permeabilization; superimposable results were obtained with notexin, taipoxin, and textilotoxin in cerebellar neurons and hippocampal neurons. Scale bar, 10 μm.

ment of PLA2 in other exocytotic events such as the sperm acrosomal exocytosis (*24*). Furthermore, a SPAN microinjected into pheochromocytoma cells inhibited neuroexocytosis (*25*), presumably because it acted on the cytosolic plasma membrane side, inducing an opposite membrane configuration. The presence of clathrin-coated Ω-shaped structures in SPAN-poisoned NMJs (*4*–*7*) suggested that they also inhibit synaptic vesicle fission from the plasma membrane (*3*, *14*). Indeed, the same SPAN-induced lipid changes promoting membrane fusion do inhibit membrane fission for the same physical and topological reasons (*17*).

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Neural Systems Responding to Degrees of Uncertainty in Human Decision-Making

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Much is known about how people make decisions under varying levels of probability (risk). Less is known about the neural basis of decision-making when probabilities are uncertain because of missing information (ambiguity). In decision theory, ambiguity about probabilities should not affect choices. Using functional brain imaging, we show that the level of ambiguity in choices correlates positively with activation in the amygdala and orbitofrontal cortex, and negatively with a striatal system. Moreover, striatal activity correlates positively with expected reward. Neurological subjects with orbitofrontal lesions were insensitive to the level of ambiguity and risk in behavioral choices. These data suggest a general neural circuit responding to degrees of uncertainty, contrary to decision theory.

In theories of choice under uncertainty used in social sciences and behavioral ecology, the only variables that should influence an uncertain choice are the judged probabilities of possible outcomes and the evaluation of those outcomes. But confidence in judged probability can vary widely. In some choices, such as gambling on a roulette wheel, probability can be confidently judged from relative frequencies, event histories, or an accepted theory. At the other extreme, such as the chance of a terrorist attack, probabilities are based on meager or conflicting evidence, where important information is clearly missing. The two types of uncertain events are often called risky and ambiguous, respectively. In subjective expected utility theory, the probabilities of outcomes should influence choices, whereas confidence about those probabilities should not. But experiments show that many people are more willing to bet on risky outcomes than on ambiguous ones, holding judged probability of outcomes constant (*1*). This empirical aversion to ambiguity motivates a search for neural distinctions between risk and ambiguity. Here, we extend the study of the neural basis of decision under risk to encompass ambiguity.

The difference between risky and ambiguous uncertainty is illustrated by the Ellsberg paradox (*2*). Imagine one deck of 20 cards composed of 10 red and 10 blue cards (the risky deck). Another deck has 20 red or blue cards, but the composition of red and blue cards is completely unknown (the ambiguous deck). A bet on a color pays a fixed sum (e.g., $10) if a card with the chosen color is drawn, and zero otherwise (Fig. 1A).

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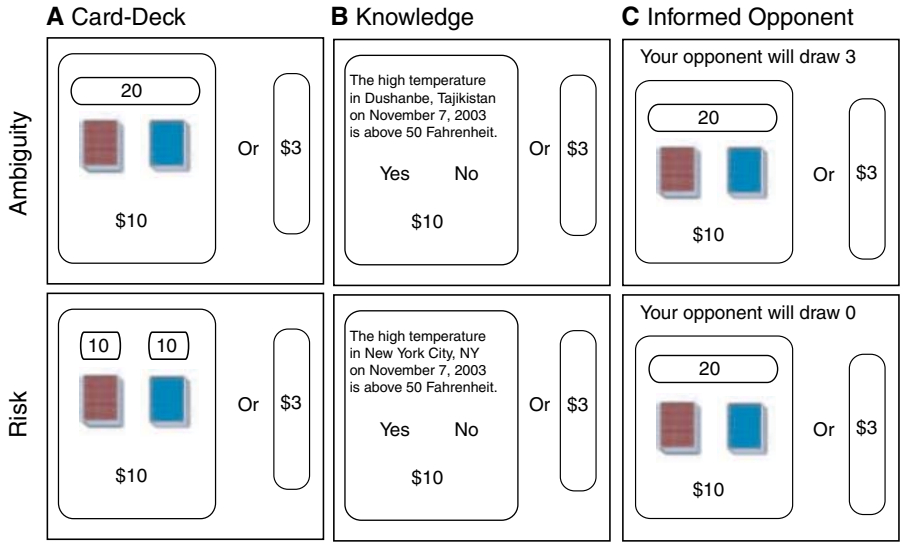

Fig. 1. Sample screens from the experiment. The conditions in the top panel are called ambiguous because the subject is missing relevant information that is available in the risk conditions (bottom panel). Subjects always choose between betting on one of the two options on the left side or taking the certain payoff on the right. (**A**) Card-Deck treatment: Ambiguity is not knowing the exact proportion; risk is knowing the number of cards (indicated by numbers above each deck). (**B**) Knowledge treatment: Ambiguity is knowing less about the uncertain events (e.g., Tajikistan) relative to risk (e.g., New York City). (**C**) Informed Opponent treatment: Ambiguity is betting against an opponent who has more information (who drew a three-card sample from the deck) than in risk (where the opponent drew no cards from the deck). Bets win if subject chooses the realized color and opponent chooses the opposite color; otherwise, both take the certain payoff [see (*17*)].

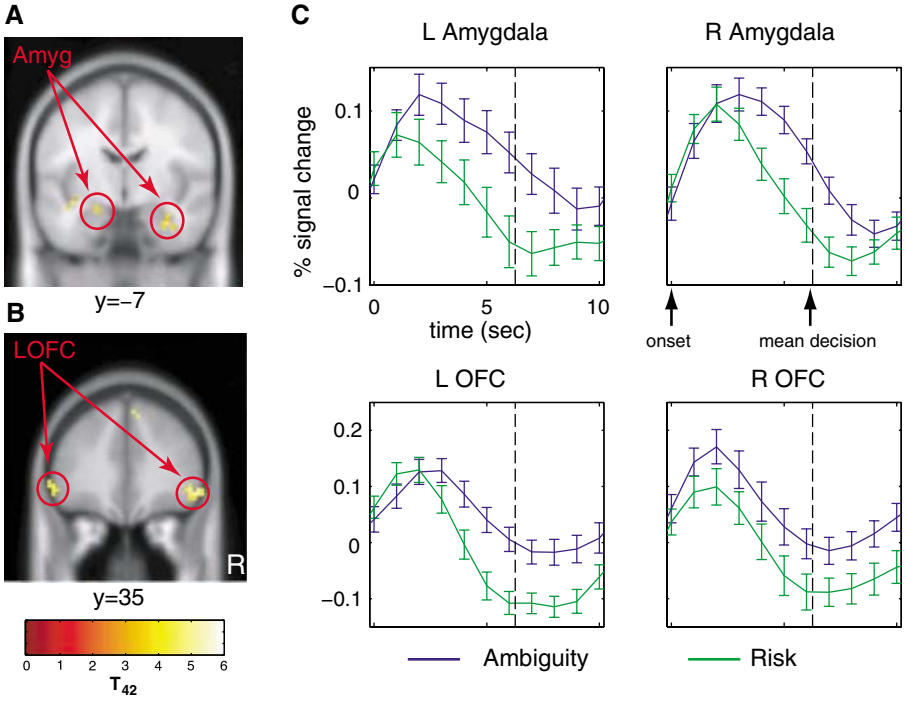

Fig. 2. Regions showing greater activation in response to ambiguity than in response to risk. Random-effects analysis of all three treatments revealed regions that are differentially activated in decision-making under ambiguity relative to risk ($P \leq 0.001$, uncorrected; cluster size $k \geq 10$ voxels). These regions include (**A**) left amygdala and right amygdala/parahippocampal gyrus (coronal section shown at $y = 7$ in MNI space; heat map represents t statistic with 42 degrees of freedom) and (**B**) bilateral OFC. (**C**) Mean time courses of amygdala and OFC (time synched to trial onset, dashed vertical lines are mean decision times; error bars are SEM; $n = 16$).

In experiments with these choices, many would rather bet on a red draw from the risky deck than on a red draw from the ambiguous deck, and similarly for blue (*3*, *4*). If betting preferences are determined only by probabilities and associated payoffs, this pattern is a paradox. In theory, disliking the bet on a red draw from the ambiguous deck implies that its subjective probability is lower [P_{amb}(red) < P_{risk}(red)]. The same aversion for the blue bets implies P_{amb}(blue) < P_{risk}(blue). But these inequalities, and the fact that the probabilities of red and blue must sum to 1 for each deck, imply $1 = P_{amb}(\text{red}) + P_{amb}(\text{blue}) < P_{risk}(\text{red}) + P_{risk}(\text{blue}) = 1$, a contradiction. The paradox can be resolved by allowing choices to depend both on subjective probabilities of events and on the ambiguity of those events (*5*–*7*). More generally, choices can depend on how much relevant information is missing or how ignorant people feel compared to others (*8*, *9*).

We explored the neural differences with varying levels of uncertainty by using a combination of data from functional magnetic resonance imaging (fMRI) and behavioral data from lesion patients. This study builds on previous findings in neuroscience on reward and uncertainty. In particular, we focus on the striatum, which has been implicated in reward anticipation (*10*); the orbitofrontal cortex (OFC), where patients with lesions perform poorly on behavioral tasks involving uncertainty, such as the Iowa gambling task (*11*); and the amygdala, which responds to ambiguous facial cues and has been hypothesized as a generalized vigilance module in the brain (*12*–*14*).

The fMRI study used three experimental treatments: The Card-Deck treatment is a baseline pitting pure risk (where probabilities are known with certainty) against pure ambiguity. The Knowledge treatment uses choices about events and facts, which fall along a spectrum from risk to ambiguity. In the Informed Opponent treatment, the subject bets against another person who has seen a sample of cards from the deck. This opponent is therefore better informed about the contents of the ambiguous deck (*15*). This condition corresponds to a commonly posited theory of ambiguity aversion: Even when there is no informed opponent, people act as if there is (*16*). All three treatments have one condition where the subject is missing information (ambiguity) relative to the other condition (risk).

Subjects made 48 choices in each treatment between certain amounts of money and bets on card decks or events (*17*). The amounts of the certain payoff and the bet payoff varied across trials. In the Card-Deck and Informed Opponent treatments, the number and proportions of cards also varied. We estimated a general linear model (GLM) using standard regression techniques (*17*). Two primary regressors were used for each treatment—one for ambiguity trials and one for risky trials—beginning at the onset of the stimulus and ending at the time of decision. To find regions differentially activated by ambiguity and risk, we performed a random-effects analysis pooling all three treatments, correcting for nonsphericity (*17*).

Regions that were more active during the ambiguous condition relative to the risk condi-

tion included the OFC and amygdala (Fig. 2A) and the dorsomedial prefrontal cortex (DMPFC) (fig. S8 and table S7). These areas have been implicated in integration of emotional and cognitive input (OFC) (*18*), reaction to emotional information (amygdala) (*19*–*21*), and modulation of amygdala activity (DMPFC) (*12*). Areas activated during the risk condition relative to ambiguity include the dorsal striatum (caudate nucleus) (Fig. 3A). Furthermore, the dorsal striatal activations were also correlated with the expected value of actual choices (Fig. 3C), whereas no such correlation was observed in the OFC or amygdala (tables S11 and S12). This, together with other studies implicating the dorsal striatum in reward prediction (*10*, *22*–*24*), supports the hypothesis that ambiguity lowers the anticipated reward of decisions.

Time courses showed different patterns of activation in the ambiguity > risk and risk > ambiguity regions. Whereas the amygdala and OFC reacted rapidly at the onset of the trial (Fig. 2C), the dorsal striatum activity built more slowly (Fig. 3B) (fig. S4) and peaked significantly later (fig. S7) than those of the amygdala and OFC. This difference was present in all three experimental treatments (figs. S3 and S4) and appeared to be independent of subjects' choices (fig. S6) (*25*). The temporal difference between these ambiguity and risk regions is consistent with the presence of two interacting systems—a "vigilance"/evaluation system in the amygdala (*26*) and OFC, which responds more rapidly to the stimuli and grades uncertainty, and a reward-anticipation system in the striatum that is further downstream.

Parameters measuring ambiguity and risk aversion (γ and ρ, respectively) were estimated from a nonlinear stochastic model of the subjects' choice behavior in our tasks (*27*). Ambiguity aversion, measured by γ, was positively correlated with contrast values between ambiguity and risk (averaged over the three treatments) in the right OFC ($r = 0.55$, $P < 0.04$, two-tailed) and more weakly in the left OFC ($r = 0.37$, $P < 0.2$, two-tailed) (*17*).

To validate the fMRI results and establish that the OFC plays a necessary role in distinguishing levels of uncertainty, we conducted behavioral experiments similar to the card-deck task above, using a lesion method (*17*). Twelve neurological subjects with focal brain lesions were partitioned into two groups: those whose lesions included the most significant activation focus in the OFC revealed in our fMRI study ($n = 5$), and a comparison group (temporal lobe damage patients) whose lesions did not overlap with any of our fMRI foci ($n = 7$). The two groups had similar etiology, IQ, mathematical ability, and performance on other background tasks (table S15).

Two-dimensional confidence interval analysis (Fig. 4) showed that frontal patients are risk- and ambiguity-neutral (i.e., the hypothesis that $\gamma = \rho = 1$ cannot be rejected). This differed from the comparison group, who appeared to be risk- and ambiguity-averse. The OFC-lesioned group therefore did not distinguish between degrees of uncertainty (ambiguity and risk). This is behaviorally abnormal but is consistent, ironically, with the logic of subjective expected utility theory.

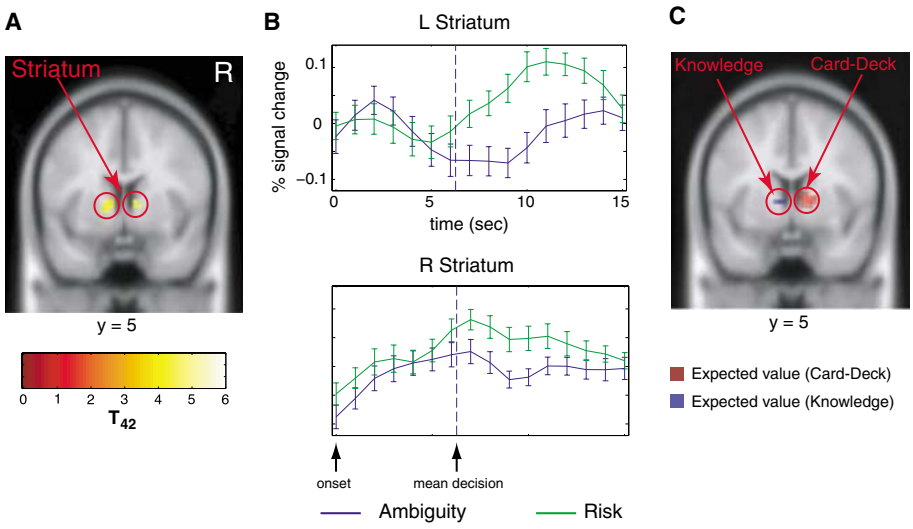

Fig. 3. Regions showing greater activation in response to risk than in response to ambiguity. Random-effects analysis of all three treatments revealed brain regions that are differentially activated in decision-making under risk. These regions include (**A**) dorsal striatum, as well as precuneus and premotor cortex (table S8) ($P \leq 0.001$, uncorrected; cluster size $k \geq 10$ voxels.) (**B**) Mean time courses for risk regions (time synched to trial onset, dashed vertical lines are mean decision times; error bars are SEM; $n = 16$). (**C**) Regions of the dorsal striatum significantly correlated with expected values of subjects' choices in risk condition of Card-Deck treatment (red) and both risk and ambiguity conditions of Knowledge treatment (blue) ($P < 0.005$, uncorrected; cluster size $k \geq 10$ voxels).

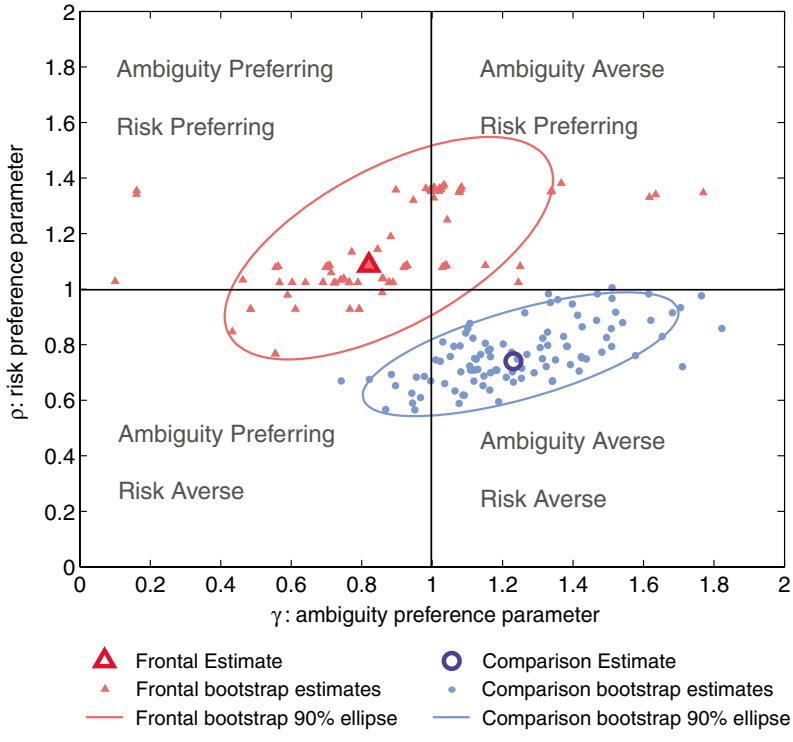

Fig. 4. Risk and ambiguity attitudes of OFC patients ($n = 5$) and lesion comparisons ($n = 7$) with associated 90% confidence intervals. The risk neutral line ($\rho = 1$) and the ambiguity neutral line ($\gamma = 1$) demarcate four quadrants as labeled. Open symbols plot maximum likelihood estimates of a group-level stochastic choice model. Frontals: ($\gamma = 0.82$, $\rho = 1.09$); lesion comparisons: ($\gamma = 1.23$, $\rho = 0.74$) [see (*17*)]. Solid symbols represent 100 bootstrapped (γ, ρ) estimates. Ellipses are two-dimensional 90% confidence intervals around the bootstrapped data. Angle of the ellipse reflects correlation between ρ and γ (0.42 for frontal, 0.31 for comparison).

Together with the fMRI results, these data suggest a neural system for evaluating general uncertainty. Both the amygdala and OFC are known to receive rapid, multimodal sensory input; both are bidirectionally connected and are known to function together in evaluating the value of stimuli (*28*); and both are likely involved in detecting salient and relevant stimuli of uncertain value. The latter function has been hypothesized especially for the amygdala (*26*, *29*). Such a function also provides a reward-related signal that can motivate behavior, by virtue of the known connections between the amygdala/OFC and the striatum (*30*). Although the circuit is assessed here in the context of a neuroeconomic experiment, we believe that it subserves general aspects of how organisms explore their environment: Under uncertainty, the brain is alerted to the fact that information is missing, that choices based on the information available therefore carry more unknown (and potentially dangerous) consequences, and that cognitive and behavioral resources must be mobilized in order to seek out additional information from the environment.

Understanding the neural basis of choice under uncertainty is important because it is a fundamental activity at every societal level, with examples as diverse as people saving for retirement, companies pricing insurance, and countries evaluating military, social, and environmental risks (*17*). The choices can vary greatly in the level of information available to the decision-maker about outcome probabilities. Standard decision theory, however, precludes agents from acting differently in the face of risk and ambiguity. Our results show that this hypothesis is wrong on both the behavioral and neural level, and suggest a unified treatment of ambiguity and risk as limiting cases of a general system evaluating uncertainty. For neuroscientists, these results introduce the important concept of varying degrees of uncertainty that is missing from previous studies of reward and decision-making. More generally, this study shows the value of combining ideas and tools from social and biological sciences (*31*, *32*).

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A Conserved Checkpoint Monitors Meiotic Chromosome Synapsis in *Caenorhabditis elegans*

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We report the discovery of a checkpoint that monitors synapsis between homologous chromosomes to ensure accurate meiotic segregation. Oocytes containing unsynapsed chromosomes selectively undergo apoptosis even if a germline DNA damage checkpoint is inactivated. This culling mechanism is specifically activated by unsynapsed pairing centers, *cis*-acting chromosome sites that are also required to promote synapsis in *Caenorhabditis elegans*. Apoptosis due to synaptic failure also requires the *C. elegans* homolog of *PCH2*, a budding yeast pachytene checkpoint gene, which suggests that this surveillance mechanism is widely conserved.

Meiosis requires two successive cell divisions: one in which homologous chromosomes separate and a second that partitions sister chromatids. Accurate segregation depends on the establishment of physical linkages (chiasmata) between homologous chromosomes during meiotic prophase. Chromosome pairing, the polymerization of the synaptonemal complex between paired homologs (synapsis), and crossover recombination are all required to generate chiasmata, which enable proper chromosome alignment on the meiotic spindle.

Defects in these early meiotic events can lead to cell cycle arrest or apoptosis, indicating that the events are monitored by checkpoints. In budding yeast, a "pachytene checkpoint" responds to defects in homolog synapsis and/or recombination [reviewed in (*1*)]. Mammalian meiosis may have two distinct checkpoints, one that responds to synaptic failure and one that responds to DNA damage (*2*–*4*). Because synapsis and recombination are obligately coupled in both *Saccharomyces cerevisiae* (*5*) and mice (*3*, *6*), it has been ambiguous whether these checkpoints are triggered by recombination defects or asynapsis. Here, we have exploited the knowledge that synapsis can be complete-

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ly uncoupled from meiotic recombination in *C. elegans* (*7*) to test whether defects in synapsis can directly trigger a meiotic checkpoint.

Each chromosome in *C. elegans* has a unique region called a pairing center (PC) that stabilizes meiotic pairing and promotes synapsis between homologs (*8*). The deficiency *meDf2* removes the PC from the X chromosome. *meDf2* homozygotes display X chromosome asynapsis in 90% of meiocytes (*8*) (Fig. 1A) and high rates of meiotic missegregation, as revealed by the frequency of male (XO) progeny (*9*). In *meDf2*/+ hermaphrodites, 60% of meiotic nuclei exhibit unsynapsed X chromosomes (*8*), but only 5 to 7% of their self-progeny are males (*9*). This discrepancy suggested that nuclei with unsynapsed X chromosomes might be culled selectively during meiosis.

About half of the oocytes in wild-type gonads undergo apoptosis (*10*). To explore the possibility that apoptosis may cull defective nuclei, we introduced mutations in the pro-apoptotic genes *ced-3* (*11*) or *ced-4* (*12*) into *meDf2*/+ hermaphrodites. *ced-3;meDf2*/+ animals produced twice as many male self-progeny as *meDf2*/+ hermaphrodites (Fig. 1B), indicating that apoptosis can enrich for normal gametes. We also quantified the fraction of oocytes that contained univalent X chromosomes during late meiotic prophase (Fig. 1C). *ced-3;meDf2*/+ hermaphrodites exhibit four times as many oocytes with achiasmate X chromosomes (Fig. 1D) as do *meDf2*/+ animals, providing additional evidence that apoptosis "filters" meiocytes to enrich for recombinant X chromosomes. When a *ced-4* mutation was introduced into *meDf2*/+ hermaphrodites, the frequencies of male self-progeny (21%) (Fig. 1B) and achiasmate X chromosomes (43%) (Fig. 1D) were even more dramatically enhanced, consistent with evidence that some apoptosis is independent of *ced-3* (*13*). Thus, meiotic nuclei with unsynapsed X chromosomes are preferentially eliminated prior to oocyte maturation.

In *C. elegans*, defects in synapsis can activate a germline DNA damage/meiotic recombination checkpoint (*14*, *15*). To determine whether this checkpoint is responsible for the death of asynaptic nuclei in *meDf2*/+ hermaphrodites, we introduced a *hus-1* (*16*) mutation into *meDf2*/+ animals (*hus-1;meDf2*/+). In contrast to *ced-3* and *ced-4*, mutation of *hus-1* did not enhance the incidence of male self-progeny (Fig. 1B) or achiasmate X chromosomes (Fig. 1D) in *meDf2*/+ hermaphrodites.

We tested whether apoptosis in *meDf2*/+ animals might result from *hus-1*–independent activation of the DNA damage/recombination checkpoint by eliminating *spo-11*, which is required for double-strand breaks (DSBs) (*7*). *spo-11* mutants produce very few viable progeny (*7*), precluding their analysis by the assays described above. Therefore, we directly quantified apoptosis in germ lines of age-matched adult hermaphrodites using a *ced-1::gfp* transgene (Fig. 2A) (*17*). Wild-type animals exhibit an average of seven apoptotic nuclei per gonad arm (Fig. 2B) as a result of physiological apoptosis that occurs during unperturbed meiosis (*10*). Mutation of *spo-11* or *hus-1* slightly reduced the number of apoptotic nuclei. Compared with wild-type, *meDf2*/+ hermaphrodites exhibited an elevated number of apoptotic nuclei (13 per gonad arm), consistent with activation of apoptosis by unsynapsed chromosomes. Moreover, this high level of apoptosis requires neither DSBs (*spo-11;meDf2*/+) nor an essential DNA damage checkpoint component (*hus-1; meDf2*/+). Elevated apoptosis in *meDf2*/+ hermaphrodites was also independent of the worm p53 homolog *cep-1* (*18*, *19*). These results reveal the activity of a previously undescribed meiotic checkpoint that activates apoptosis in response to defects in synapsis (Fig. 2C).

Because *meDf2* homozygotes show even higher levels of X chromosome asynapsis than *meDf2*/+ hermaphrodites, we were not surprised to detect elevated apoptosis in these animals (Fig. 3A). However, when mutations in *spo-11* or *hus-1* were introduced into *meDf2* homozygotes, germline apoptosis was restored to wild-type levels (Fig. 3A). Thus, in *meDf2* homozygotes, elevated apoptosis requires the DNA damage checkpoint, which indicates that the synapsis checkpoint is not activated. This suggested that the checkpoint might be specifically triggered by unsynapsed PCs, because half of the unsynapsed chromosomes in *meDf2*/+ hermaphrodites carry functional PCs, whereas *meDf2* homozygotes lack unsynapsed PCs. We therefore investigated the effects of *him-8* mutations. HIM-8 localizes to the X chromosome PC and is required for its roles in homolog pairing and synapsis (*20*). Like *meDf2* homozygotes, *him-8* mutants show high levels of apoptosis that strictly depend on the DNA damage checkpoint (Fig. 3A). Furthermore, in *him-8;meDf2*/+ hermaphrodites, elevated apoptosis requires *hus-1* (Fig. 3A). HIM-8 is therefore required for unsynapsed X chromosomes to activate the DNA-damage–independent synapsis checkpoint, supporting the hypothesis that the PC plays an essential role in this mechanism. The complementary functions of these sites in both promoting synapsis and detecting defects in this process are evocative of the involvement of centromeres in both microtubule attachment and the spindle assembly checkpoint.

The X chromosome in *C. elegans* has many distinct features (*21*–*24*), including its lack of a meiotic partner in males. We therefore tested whether unsynapsed autosomes can also trigger the synapsis checkpoint. Mutation of the

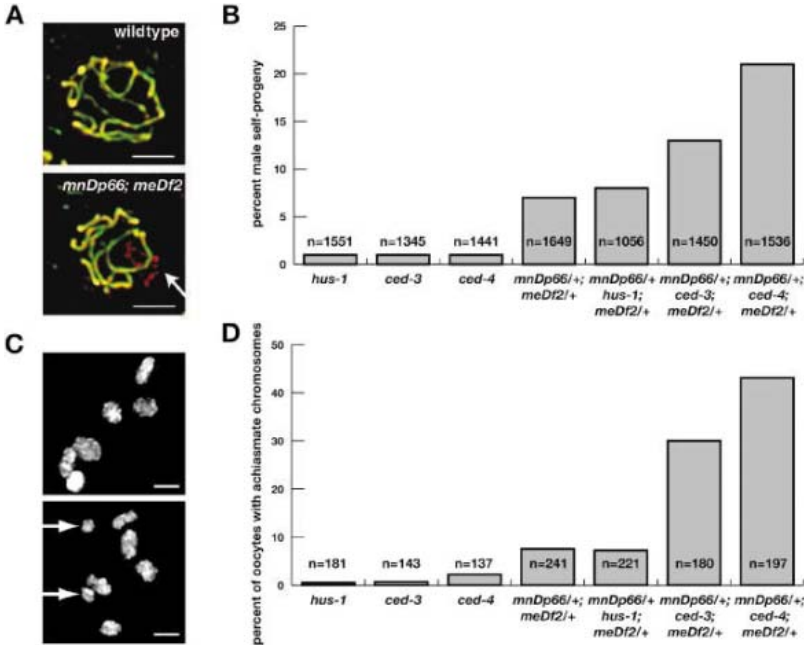

Fig. 1. Apoptosis preferentially eliminates meiocytes with unsynapsed chromosomes. (**A**) Unsynapsed X chromosomes in *meDf2* pachytene nuclei are visualized as segments of HTP-3 (red) staining devoid of SYP-1 (green). *mnDp66* is a duplication required for the viability of *meDf2* homo- and hemizygotes (*30*). Scale bars, 2 μm. (**B**) X chromosome nondisjunction in *meDf2*/+ hermaphrodites is elevated by mutations in core apoptotic components but not a DNA damage checkpoint gene. Differences between *meDf2*/+ and *ced-3;meDf2*/+ or *ced-4;meDf2*/+ are significant ($P < 0.0001$). (**C**) Achiasmate chromosomes in mature oocytes. Six DAPI (4′,6′-diamidino-2-phenylindole)–stained bodies in the oocyte in the top image represent the six recombinant bivalents, whereas the lower image shows five autosomal bivalents and two achiasmate X chromosomes (arrows). (**D**) Culling of nuclei with unsynapsed chromosomes precedes oocyte maturation. Mutation of *ced-3* or *ced-4* in *meDf2*/+ hermaphrodites results in a higher fraction of mature oocytes with achiasmate X chromosomes. Differences between *meDf2*/+ and *ced-3;meDf2*/+ or *ced-4;meDf2*/+ are significant ($P < 0.0001$).

synaptonemal complex genes *syp-1* and *syp-2* results in asynapsis of all chromosomes and very high levels of apoptosis (*14*, *15*); CED-1-GFP revealed an average of 23 corpses per gonad arm in *syp-1* mutants (Fig. 3B). When DSBs are eliminated (i.e., *spo-11;syp-1*), apoptosis is reduced, but not to wild-type levels (*14*) (Fig. 3B). We detected elevated levels of apoptosis in *spo-11;syp-1;meDf2* triple-mutant hermaphrodites (Fig. 3B), indicating that the synapsis checkpoint is activated in the absence of DSBs and the X chromosome PC. Thus, the synapsis checkpoint monitors the synapsis of all chromosomes, likely through their PCs.

These experiments also illustrate that the synapsis checkpoint is fully activated whether one pair (*meDf2*/+) or all homolog pairs (*spo-11;syp-1*) are unsynapsed. A similar phenomenon has been observed in mice (*4*). Our experiments also suggest that this checkpoint is saturable, unlike the DNA damage/recombination checkpoint, which exhibits clear dose-dependence (*25*). The checkpoint responds similarly whether all the nuclei in the germline exhibit homolog asynapsis or only 60% have unsynapsed chromosomes.

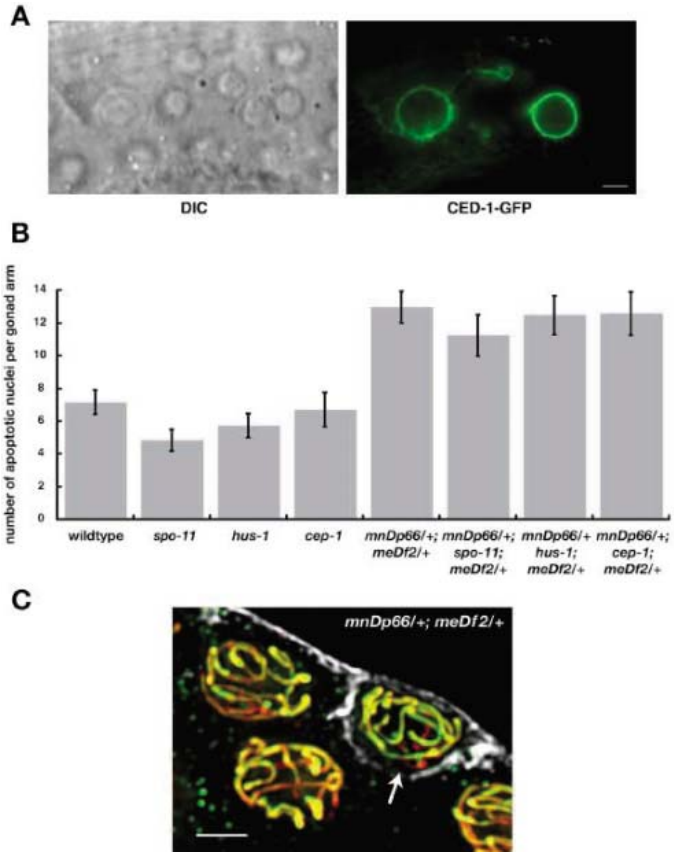

Fig. 2. Activation of apoptosis in *meDf2*/+ hermaphrodites is independent of DSBs and the DNA damage checkpoint. (**A**) CED-1-GFP identifies germline apoptotic nuclei. Differential interference contrast (DIC) and fluorescent images of apoptotic nuclei in the germline of wild-type animals expressing a CED-1-GFP fusion protein. (**B**) Mutation of *spo-11*, *hus-1*, or *cep-1* does not affect the number of apoptotic nuclei in *meDf2*/+ hermaphrodites. Error bars, ±2 × SEM. (**C**) Asynapsis of a single pair of chromosomes causes apoptosis. Meiotic nuclei in a *meDf2*/+ hermaphrodite stained for SYP-1 (green), HTP-3 (red), and GFP (white). The nucleus encircled by CED-1-GFP contains a pair of unsynapsed chromosomes. Surrounding nuclei show complete synapsis and lack CED-1-GFP.

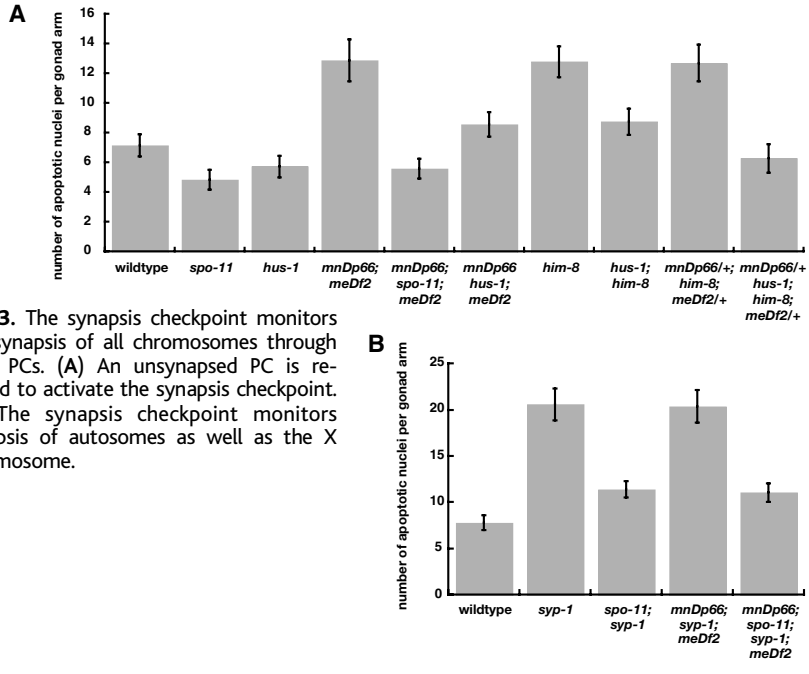

Fig. 3. The synapsis checkpoint monitors the synapsis of all chromosomes through their PCs. (**A**) An unsynapsed PC is required to activate the synapsis checkpoint. (**B**) The synapsis checkpoint monitors synapsis of autosomes as well as the X chromosome.

PCH2 encodes an AAA–adenosine triphosphatase (AAA-ATPase) essential for the pachytene checkpoint in budding yeast (*26*). The predicted gene *F10B5.5* encodes a candidate worm ortholog, based on its sequence similarity and elevated germline expression (*27*). We analyzed a deletion allele, *pch-2(tm1458),* to evaluate the role of this gene during meiosis. In *pch-2;meDf2*/+ hermaphrodites, we observed wild-type levels of apoptotic nuclei per gonad arm (Fig. 4A), consistent with an essential role for this gene in the synapsis checkpoint. In contrast, we found that *pch-2* does not reduce the number of apoptotic nuclei in either *him-8* or *meDf2* homozygous animals (Fig. 4A), indicating that it is dispensable for the germline DNA damage/recombination checkpoint. We also combined the *pch-2(tm1458)* allele with a *syp-1* mutation. Like *spo-11;syp-1* double mutants, *pch-2;syp-1* double mutants exhibit intermediate levels of apoptosis (Fig. 4B), suggesting a defect in one of the two meiotic checkpoints but not both. In *pch-2;spo-11;syp-1* triple mutants, apoptosis falls to wild-type levels (Fig. 4B), reinforcing the conclusion that *pch-2* is specifically required for *spo-11*–independent checkpoint activation. These results support a role for the *pch-2* gene in the synapsis checkpoint, but not the recombination checkpoint, in *C. elegans* (fig. S3).

It is perplexing that *meDf2*/+ hermaphrodites exhibit persistent recombination intermediates on their unsynapsed chromosomes (*8*), yet they fail to activate the DNA damage/recombination checkpoint (Fig. 1, B and D, and Fig. 2B), even in the absence of *pch-2* (Fig. 4 and fig. S1). We propose that an unsynapsed PC can inhibit activation of the DNA damage/recombination checkpoint but that this can be overcome by sufficient levels of unprocessed DSBs, e.g., in *syp-1* mutants with fully unsynapsed chromosomes.

SPO11 function is necessary to activate the pachytene checkpoint in budding yeast, which has led to the idea that the checkpoint may monitor persistent recombination intermediates (*1*). However, Spo11p plays additional, nonenzymatic roles during meiosis (*28*), raising the possibility that *SPO11*-dependent chromosomal features, rather than DSBs per se, may be required for checkpoint activation. Moreover, mutation of *PCH2* alleviates the meiotic arrest of some mutants (*zip1* and *dmc1*) but not others (*hop2*) (*1*), suggesting that the yeast "pachytene checkpoint" may actually be an amalgamation

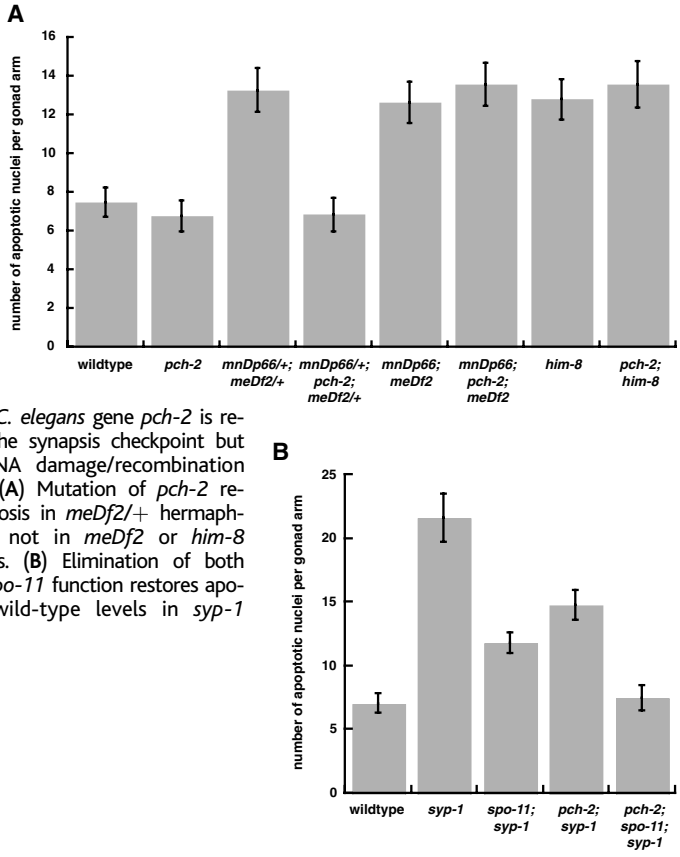

Fig. 4. The *C. elegans* gene *pch-2* is required for the synapsis checkpoint but not the DNA damage/recombination checkpoint. (**A**) Mutation of *pch-2* reduces apoptosis in *meDf2*/+ hermaphrodites but not in *meDf2* or *him-8* homozygotes. (**B**) Elimination of both *pch-2* and *spo-11* function restores apoptosis to wild-type levels in *syp-1* mutants.

of checkpoints. In light of our evidence for conservation of *pch-2* function from yeast to worms, defects in synapsis may also directly trigger meiotic arrest in budding yeast.

Unsynapsed sex chromosomes can activate a p53-independent meiotic checkpoint in mammals (*2*). Moreover, *Spo11*$^{-/-}$ mutant mice still exhibit spermatocyte death (*3*) and oocyte loss that is distinguishable from the apoptosis induced by mutations of DSB processing enzymes (*4*). Although direct experimental evidence is still lacking, it is likely that some loss of gametes in *Spo11*$^{-/-}$ mutant mice may result from their synaptic failures.

Our results demonstrate that synapsis can be monitored independently of recombination defects to ensure the accuracy of the meiotic divisions and prevent the production of aneuploid gametes. Further elucidation of this mechanism in *C. elegans* will likely shed light on the basis of human infertility, particularly in males, which has been linked to synaptic defects during meiotic prophase (*29*).

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Snapshot of Activated G Proteins at the Membrane: The $G\alpha_q$-GRK2-$G\beta\gamma$ Complex

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G protein–coupled receptor kinase 2 (GRK2) plays a key role in the desensitization of G protein–coupled receptor signaling by phosphorylating activated heptahelical receptors and by sequestering heterotrimeric G proteins. We report the atomic structure of GRK2 in complex with $G\alpha_q$ and $G\beta\gamma$, in which the activated $G\alpha$ subunit of G_q is fully dissociated from $G\beta\gamma$ and dramatically reoriented from its position in the inactive $G\alpha\beta\gamma$ heterotrimer. $G\alpha_q$ forms an effector-like interaction with the GRK2 regulator of G protein signaling (RGS) homology domain that is distinct from and does not overlap with that used to bind RGS proteins such as RGS4.

G protein–coupled receptors (GPCRs) are involved in a vast array of physiological processes, and the molecular basis for how signals are passed from activated receptors, through heterotrimeric G proteins ($G\alpha\beta\gamma$), and then to downstream effectors has been the subject of intense investigation (*1*, *2*). Crystal structures of inactive rhodopsin (*3*, *4*) and the $G\alpha\beta\gamma$ heterotrimer (*5*, *6*) have been determined, as have structures of activated $G\alpha$ and $G\beta\gamma$ subunits

bound to various effector targets (*7*–*10*). These atomic models provide the first and last frames, respectively, of a molecular signaling movie that describes the course of heterotrimeric G protein signaling. The three switch regions of the Gα subunit play key roles, changing conformation depending on whether guanosine diphosphate (GDP) or guanosine triphosphate (GTP) is bound. In the Gαβγ heterotrimer, Gα is bound to GDP, and switch II is sequestered by Gβγ (Fig. 1, A and B). On activation of Gα, GTP is bound; switch II dissociates from Gβγ; and switches I, II, and III adopt a conformation appropriate for binding effectors and RGS proteins (*7*, *11*, *12*). The events that occur between the first and last frames of this molecular signaling movie are not well understood. Although receptor recognition of Gαβγ appears to be mediated primarily by the C-terminal region of the Gα subunit (*13*, *14*), fundamental issues remain unresolved, including how activated GPCRs manipulate Gαβγ to mediate nucleotide exchange on Gα (*15*, *16*); whether Gα, Gβγ, and GPCRs remain associated after activation (*17*–*19*); and how G protein subunits and their effector complexes are arranged at the membrane during signal transduction.

G protein–coupled receptor kinase 2 (GRK2) initiates phosphorylation-dependent desensitization of GPCRs (*20*, *21*) by phosphorylating the C-terminal tail or third intracellular loop of activated GPCRs (*22*). GRK2 also can inhibit GPCR signaling via phosphorylation-independent mechanisms (*23*, *24*), including sequestration of $G\alpha_{q/11/14}$ subunits with its RGS homology (RH) domain (*25*–*28*) and Gβγ with its pleckstrin homology (PH) domain (*29*, *30*). The crystallographic structure of GRK2 in complex with Gβγ suggested that the arrangement of its kinase, RH, and PH domains is compatible with the simultaneous recognition of activated receptor, $G\alpha_q$, and Gβγ, respectively (*9*). The structure of a $G\alpha_q$-GRK2-Gβγ complex should therefore reveal the configuration of Gα and Gβγ subunits as they engage a single protein target and provides another snapshot of the events that unfold after GPCR activation.

$G\alpha_q$ was overexpressed in insect cells as a soluble chimera (henceforth referred to as $G\alpha_{i/q}$) in which the wild-type N-terminal helix was replaced with that of $G\alpha_{i1}$ (*31*, *32*). $G\alpha_{i/q}$ bound GRK2 in an AlF_4^--dependent manner (fig. S1), and the resulting $G\alpha_{i/q}$·GDP·Mg^{2+}·AlF_4^--GRK2 complex could be crystallized in the presence of a soluble mutant of $G\beta_1\gamma_2$ (fig. S2). The resulting $G\alpha_{i/q}$-GRK2-Gβγ complex was solved by molecular replacement with the use of x-ray diffraction data extending to 3.1 and 4.5 Å spacings in the best and worst reciprocal lattice directions, respectively (table S1) (*31*).

In the $G\alpha_{i/q}$-GRK2-Gβγ complex, GRK2 serves as a scaffold for the activated heterotrimeric G proteins, with $G\alpha_{i/q}$·GDP·Mg^{2+}·AlF_4^- bound to the RH domain and Gβγ bound to the PH domain (Fig. 1, C and D). The switch regions of $G\alpha_{i/q}$ adopt a conformation typical of other activated Gα subunits (fig. S3), and $G\alpha_{i/q}$-bound GRK2-Gβγ differs only subtly from GRK2-Gβγ alone (see supporting online text). The Gα subunit, however, undergoes a dramatic ~105° rotation from its position in the Gαβγ heterotrimer to engage GRK2 (Figs. 1 and 2; movies S1 and S2). In doing so, the regions of Gα believed to be adjacent to the membrane in Gαβγ (i.e., the N and C termini) are rotated away, such that switch I, switch II, linker 1, and the αB-αC loop are closest to the predicted membrane surface, although ~30 Å removed (Fig. 2). It is not clear whether this reorientation of $G\alpha_{i/q}$ is GRK2-specific or if it could also represent the position of other activated, effector-bound Gα subunits at the membrane. We note that whereas structures of $G\alpha_t$ in complex with phosphodiesterase-γ (PDEγ) and $G\alpha_{13}$ in complex with p115-Rho guanine nucleotide exchange factor (p115RhoGEF) are compatible with the predicted membrane surface when superimposed on GRK2-bound $G\alpha_{i/q}$, the $G\alpha_s$–adenylyl cyclase complex is not (*7*, *8*, *10*). Gβγ also undergoes an apparent ~22° rotation from its position in the Gαβγ heterotrimer (compare Fig. 1, A and C), which was also evident in the GRK2-Gβγ structure (*9*).

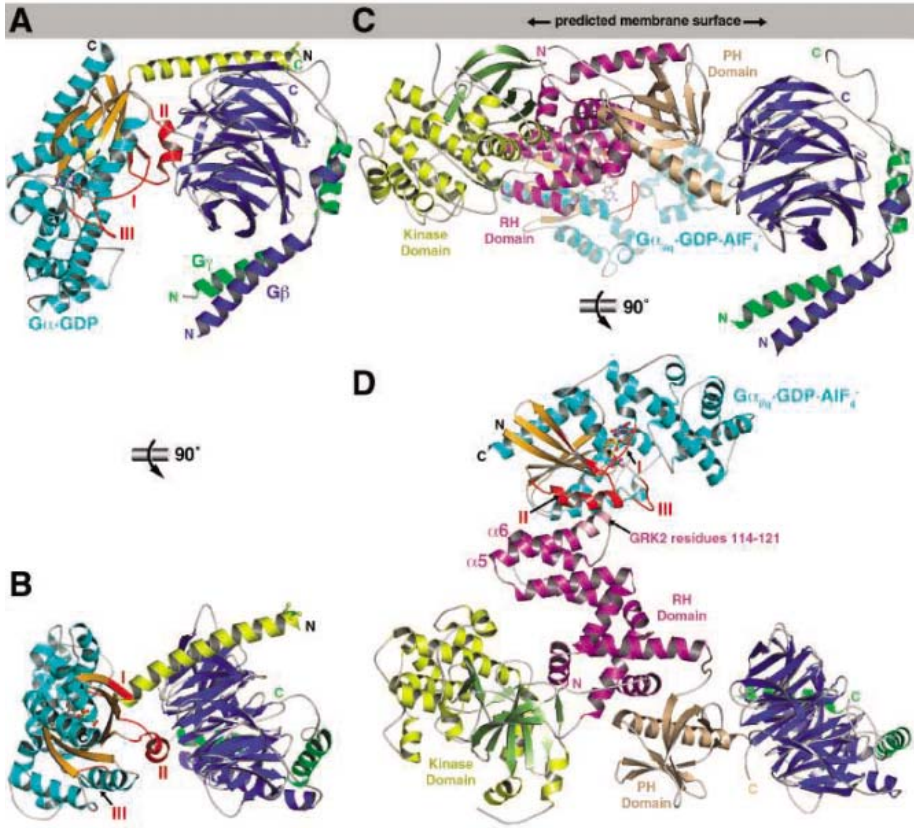

Fig. 1. Comparison of the inactive Gαβγ heterotrimer and the $G\alpha_{i/q}$-GRK2-Gβγ complex. (**A**) Side view of $G\alpha_q\beta\gamma$. $G\alpha_q\beta\gamma$ was homology modeled by using the structure of $G\alpha_i\beta_1\gamma_2$ (*5*). The expected membrane surface is modeled as a gray rectangle that extends out from the plane of the figure (*31*), and the heterotrimer is oriented as proposed in (*6*). $G\alpha_q$ is cyan with orange β-strands, Gβ is blue, and Gγ is green. The three switch regions (labeled I, II, and III) and the N-terminal helix of $G\alpha_q$ are red and yellow, respectively. GDP and $G\alpha_q$-Cys^9 and Cys^{10}, which can be palmitoylated, are shown as ball-and-stick models. (**B**) Top view of $G\alpha_q\beta\gamma$ from the perspective of the modeled membrane surface. (**C**) Side view of the $G\alpha_{i/q}$-GRK2-Gβγ complex. For purposes of comparison, GRK2-bound Gβγ was centered in the same position as Gβγ in panel (A). The chimeric N-terminal helix of GRK2-bound $G\alpha_{i/q}$ is disordered in the crystal structure. The kinase domain of GRK2 is yellow with olive β strands, the RH domain is purple, and the PH domain is tan. Mg^{2+} (black sphere) and AlF_4^- (green and magenta) are bound in the active site of $G\alpha_{i/q}$. (**D**) Top view of the $G\alpha_{i/q}$-GRK2-Gβγ complex from the same orientation as (B). Residues 114 to 121 in α5 of GRK2 (shaded pink) alter their conformation upon docking with the effector-binding pocket of $G\alpha_{i/q}$ (see SOM text).

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In Gαβγ, the N terminus of Gα forms a single, extended α helix that interacts with Gβ and, presumably, with the membrane via basic residues and/or lipid modifications (Fig. 1, A and B) (*5*, *6*, *33*). Interpreting the role of this helix in our structure is problematic because it is both chimeric and disordered. However, the first observed residue of $G\alpha_{i/q}$, corresponding to $G\alpha_q$-Arg^{38}, is sufficiently removed from the predicted membrane surface (~30 Å) and from its position in the Gαβγ heterotrimer (~80 Å) to suggest that the N-terminal helix is at least partially dissociated from the membrane and completely dissociated from Gβγ (Fig. 2).

The $G\alpha_{i/q}$-GRK2 interface buries ~1700 $Å^2$ of accessible surface area and involves α2 (switch II), α3, and the α3-β5 loop of $G\alpha_{i/q}$, as well as the α5 and α6 helices of the GRK2 RH domain (Figs. 1D and 3A). Within the interface, hydrogen bonds are formed between the hydroxyl of $G\alpha_q$-Tyr^{261} and the side chains of GRK2-Asp^{110} and -Arg^{106}, as well

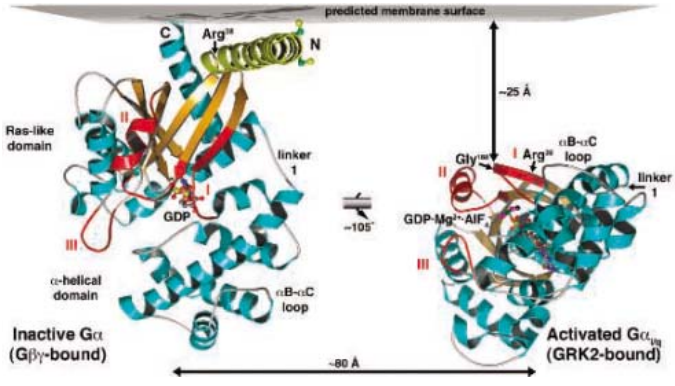

Fig. 2. Changes in the orientation of $G\alpha_q$ on activation and binding of GRK2. The model of Gβγ-bound $G\alpha_q$·GDP and the structure of GRK2-bound $G\alpha_{i/q}$·GDP·Mg^{2+}·AlF_4^- are viewed from a direction roughly 90° around a vertical axis from those of Fig. 1, A and C, respectively. The Gα subunits were positioned by translationally centering the Gβγ subunits of their respective complexes along the plane of the modeled membrane (Fig. 1). On binding GRK2, $G\alpha_{i/q}$ rotates by ~105° such that Gly^{188} in switch I of GRK2-bound $G\alpha_{i/q}$ becomes the closest residue to the modeled membrane surface (~25 Å below). The most N-terminal residue observed in GRK2-bound $G\alpha_{i/q}$, Arg^{38}, which is expected to be adjacent to the membrane in Gαβγ, is displaced by ~30 Å from the membrane. However, the native N-terminal helix of $G\alpha_q$ is sufficiently long (37 residues, ~55 Å long) to allow the palmitoylation sites at Cys^9 and Cys^{10} to be adjacent to the membrane. If one assumes that Gα and Gβγ derive from a single heterotrimer, $G\alpha_q$-Arg^{38} also translates ~80 Å away from its position in the Gαβγ heterotrimer (Fig. 2), and the fully extended wild-type N-terminal helix of $G\alpha_q$ would fall short of contacting Gβγ. Therefore, activated $G\alpha_q$ dissociates partially, if not completely, from the membrane and entirely from Gβγ, at least when in complex with GRK2.

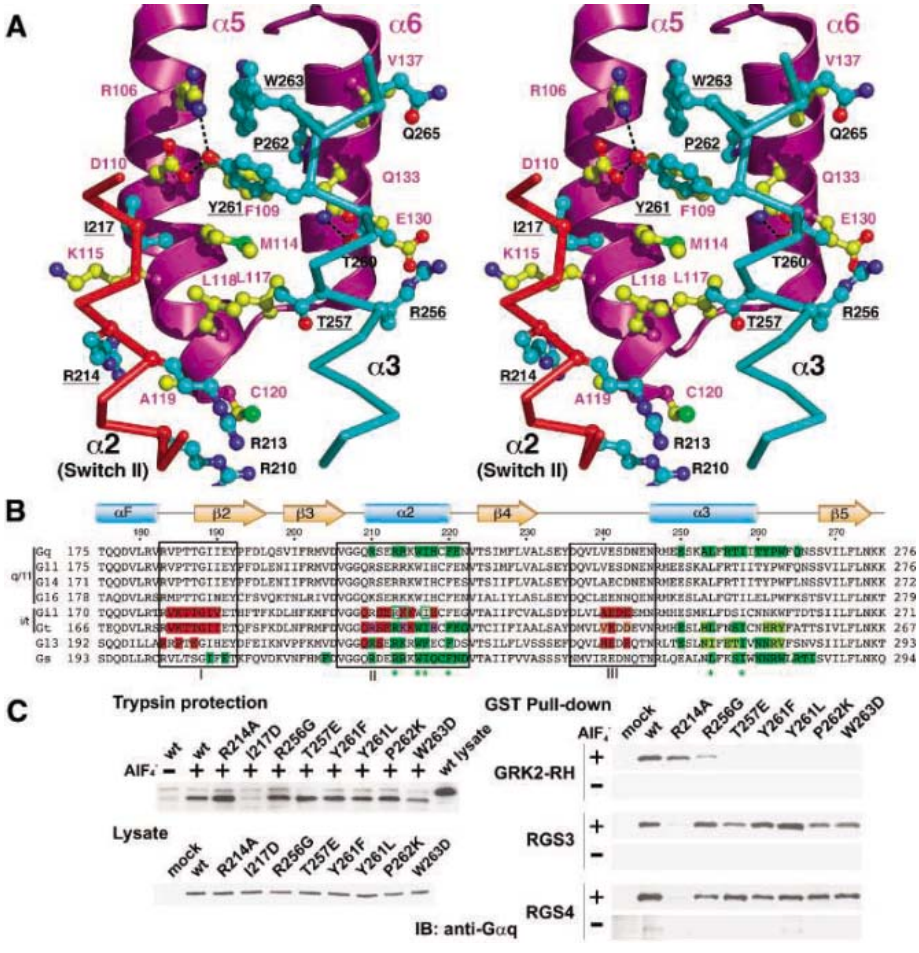

Fig. 3. The GRK2-binding surface of $G\alpha_q$. (**A**) Stereoview of the interface. The switch II and α3 helices from $G\alpha_{i/q}$ are shown as Cα traces; the α5 and α6 helices from GRK2 are shown as cartoon ribbons. Side chains of interfacial residues are shown as ball-and-stick models, with carbon atoms from $G\alpha_{i/q}$ and GRK2 colored cyan and yellow, respectively. Hydrogen bonds are shown as dashed black lines. Residues targeted by site-directed mutagenesis in this study are underlined. (**B**) Sequence alignment of the switch regions and the α3/β5 sequence for representative members of all four Gα subfamilies. Switch regions (I to III) are outlined in black and are assigned on the basis of comparison of the active and deactivated structures of $G\alpha_{i1}$. Secondary structure is represented by cylinders and arrows for α helices and β strands, respectively. Gα residues that contact effectors are green, those that bind GAPs are red, and those that contact both are purple. Contacting residues that were chimeric (i.e., nonnative) in the crystal structures of the $G\alpha_t$ and $G\alpha_{13}$ effector complexes are shown in a lighter shade of the appropriate color. Green boxes outline $G\alpha_i$ residues proposed to interact with adenylyl cyclase (*50*), and asterisks indicate conserved residues that contribute to the hydrophobic effector-binding pocket. The crystal structures used for these assignments are those of $G\alpha_{i/q}$-GRK2-Gβγ (this study), $G\alpha_i$-RGS4 [Protein Data Bank (PDB) code 1AGR] (*12*), $G\alpha_t$-PDEγ-RGS9 (1FQJ) (*8*), $G\alpha_{13}$-p115RhoGEF (1SHZ) (*10*), and $G\alpha_s$-adenylyl cyclase (1AZS) (*7*). The sequences are those of mouse $G\alpha_q$ (M55412), mouse $G\alpha_{11}$ (NP_034431), mouse $G\alpha_{14}$ (NP_032163), human $G\alpha_{16}$ (M63904), rat $G\alpha_{i1}$ (M17527), bovine $G\alpha_t$ (P04695), mouse $G\alpha_{13}$ (NP_034433), and bovine $G\alpha_s$ (M13006). (**C**) Mutational analysis of $G\alpha_q$ residues that directly interact with GRK2. Lysates of HEK293 cells expressing $G\alpha_q$ mutants were subjected to limited trypsin digestion in the presence and absence (shown only for wild type) of AlF_4^- and immunoblotted with $G\alpha_q$-specific antibody (upper left) (*31*). The I217D mutation could not be protected from trypsin digestion and was judged nonfunctional. All $G\alpha_q$ mutants expressed at a similar level compared with wild-type $G\alpha_q$ (lower left). Pull-down assays were performed by incubating lysates with 40 nM glutathione *S*-transferase (GST) fusion protein of either GRK2-RH, RGS3 (amino acids 313 to 519), or RGS4 either in the presence or absence of AlF_4^- and then detecting bound $G\alpha_q$ with $G\alpha_q$-specific antibody (right).

as between the side chains of $G\alpha_q$-Thr^{260} and GRK2-Gln^{133}. The primary nonpolar interactions are made by the side chains of GRK2-Met^{114}, Leu^{117}, Leu^{118}, and Cys^{120}, which dock into a cleft formed between the α2 (switch II) and α3 helices of $G\alpha_{i/q}$. The residues of GRK2 that form the interface with $G\alpha_{i/q}$ are essentially the same as those identified in previous studies, wherein mutation of Asp^{110}, Arg^{106}, and Leu^{118} of the GRK2 RH domain eliminated $G\alpha_q$ binding (*34*, *35*). Furthermore, the D110A mutation in GRK2 abrogates its ability to mediate phosphorylation-independent desensitization in vivo (*36*, *37*). The GRK2-binding residues of $G\alpha_{i/q}$ are analogous to those in $G\alpha_s$ and $G\alpha_t$ that bind adenylyl cyclase and PDEγ, respectively (*7*, *8*), and are among those previously implicated in the binding of phospholipase C–β (PLC-β) (*38*, *39*). Thus, the GRK2 RH domain binds $G\alpha_{i/q}$ more like an effector than an RGS protein (*8*, *12*) (Fig. 3B), a result that is consistent with the facts that GRK2 efficiently binds $G\alpha_q$·GTPγS and does not exhibit significant guanosine triphosphatase (GTPase)–activating protein (GAP) activity toward $G\alpha_q$ (*25*). Residues in switches I and III of $G\alpha_q$ previously implicated in binding GRK2 (*35*) appear to play only an indirect role, perhaps by altering the structure or dynamics of switch II.

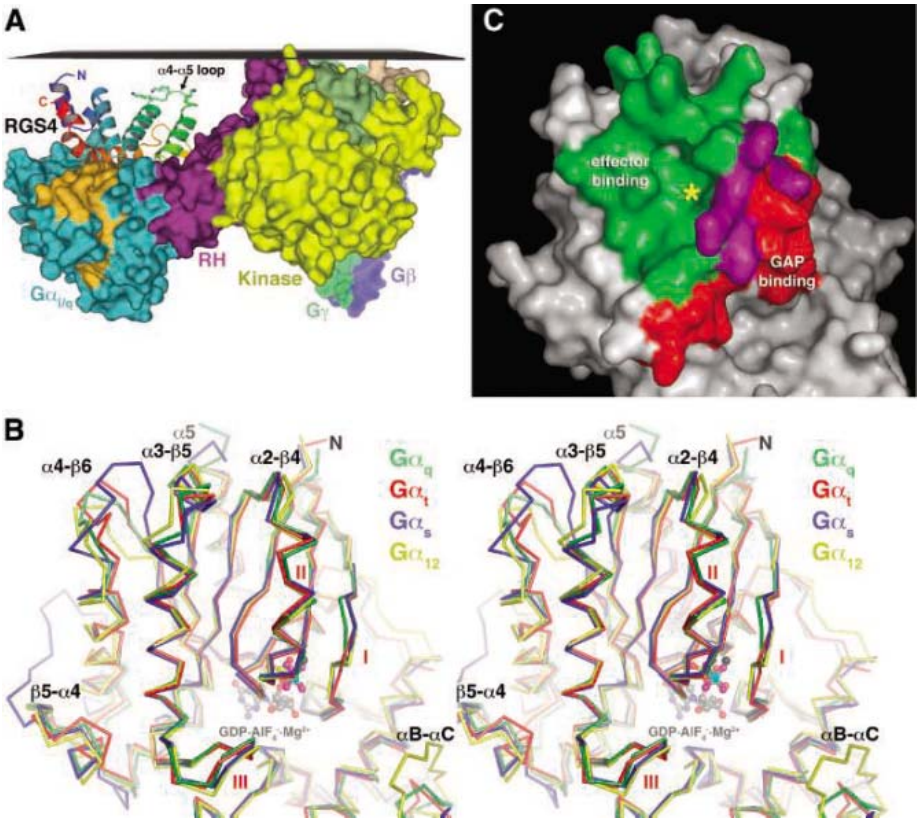

Fig. 4. Comparison of effector and GAP-binding sites among the four Gα subfamilies. (**A**) Model of RGS4 bound to the $G\alpha_{i/q}$-GRK2-Gβγ complex. RGS4 was positioned by superimposing $G\alpha_i$ of the $G\alpha_i$-RGS4 complex (*12*) with $G\alpha_{i/q}$. The docked RGS4 has no obvious steric overlaps with GRK2. The α4-α5 loop and the N-terminal region of RGS4, which are both believed to interact with the cell membrane (*51*, *52*), are juxtaposed with the membrane surface modeled for the $G\alpha_{i/q}$-GRK2-Gβγ complex. The $G\alpha_{i/q}$-GRK2-Gβγ complex is shown as a molecular surface with the same colors as in Fig. 1, except that the switch regions of $G\alpha_{i/q}$ are not highlighted. RGS4 is colored in a spectrum from blue to red from its observed N and C termini (residues 51 and 178, respectively). The side chains of basic residues in its α4-α5 loop believed to interact with phosphatidylinositol 3,4,5-trisphosphate (PIP_3) (*51*), are shown as ball-and-stick models. (**B**) Structural alignment of Ras-like domains of activated Gα subunits. The region of Gα that encompasses the three switch regions was used for the alignment: $G\alpha_q$ (this study, green), residues 183 to 261; $G\alpha_t$ (PDB code 1TAD, red), residues 174 to 252 (*53*); $G\alpha_s$ (1AZS, blue), residues 201 to 279 (*7*); and $G\alpha_{12}$ (1ZCA, yellow), residues 203 to 281 (*32*). The structure of activated $G\alpha_{12}$ is used to represent the $G\alpha_{12/13}$ family, because the $G\alpha_{13}$ protein used in the p115RhoGEF complex is a $G\alpha_{i1}$ chimera within the effector-binding region (*10*). Overall, $G\alpha_q$ is most similar to $G\alpha_i$ and $G\alpha_t$ (root mean square deviation of 1.0 Å for 303 analogous C^α positions). The most structurally heterogeneous regions of $G\alpha_q$ are the β5-α4 and α4-β6 loops in the Ras-like domain and, in the α-helical domain, the αB-αC loop. The distinct structures of the α4-β6 and αB-αC loops may allow for specific recognition of Gα subunits by receptors or guanine-nucleotide exchange inhibitors, respectively (*2*, *54*). In contrast, the tertiary structures of the switch regions, which dictate effector and GAP protein interactions, are well conserved. (**C**) Footprints of effector and GAP-binding sites on the molecular surface of $G\alpha_{i/q}$. Colors are assigned as in Fig. 3B. The yellow asterisk indicates the position of the hydrophobic pocket used by all characterized Gα effectors. As originally proposed on inspection of the $G\alpha_s$-adenylyl cyclase complex (*7*, *55*), effectors and GAPs have apparently evolved to bind to distinct and generally nonoverlapping regions of the Gα subunit. Although the residues colored purple imply steric overlap, different surfaces of these residues are used to bind effectors and GAPs.

The R214A, I217D, T257E, Y261F, and W263D mutants of $G\alpha_q$ (*40*) were generated to test the importance of these positions for binding GRK2 (Fig. 3C). The $G\alpha_q$-T257E, $G\alpha_q$-Y261F, and $G\alpha_q$-W263D mutants completely abrogated binding, whereas the $G\alpha_q$-R214A mutant retained its interaction with the GRK2 RH domain, and the I217D mutant was nonfunctional (Fig. 3C). The complete loss of binding caused by the subtle Y261F mutation emphasizes the importance of the hydrogen bonds formed by the hydroxyl of $G\alpha_q$-Tyr^{261}. Previously, it was shown that the $G\alpha_q$-I259A/T260A/Y261A mutant stimulates PLC-β similarly to wild type and that the $G\alpha_q$-R256A/T257A mutant is deficient (*39*). Therefore, whereas GRK2 and PLC-β bind overlapping regions on $G\alpha_q$, the residues of $G\alpha_q$ most critical for binding differ.

Next, the $G\alpha_q$-P262K, R256G, and Y261L mutants were created to test the role of these positions in dictating specificity of $G\alpha_q$ for GRK2 (Fig. 3B). In other Gα subfamilies, the residue equivalent to $G\alpha_q$-Pro^{262}, which packs between $G\alpha_q$-Trp^{263}, GRK2-Leu^{136}, and GRK2-Val^{137} (Fig. 3A), is replaced by either arginine or lysine. As expected, the $G\alpha_q$-P262K mutation abolished GRK2 binding (Fig. 3C). The $G\alpha_q$-R256G and $G\alpha_q$-Y261L mutants represent conversions of these residues to their equivalents in $G\alpha_{16}$ (Fig. 3B), which does not bind GRK2 (*28*). The R256G mutation significantly reduced binding, whereas the $G\alpha_q$-Y261L substitution eliminated binding (Fig. 3C). Therefore, residues 261 to 263 of $G\alpha_q$, and their equivalents in $G\alpha_{11}$ and $G\alpha_{14}$, appear sufficient to dictate the Gα specificity of GRK2.

The $G\alpha_q$-R214A mutation in switch II completely abolished binding to RGS3 and RGS4, but not to GRK2, emphasizing the importance of $G\alpha_q$-Arg^{214} in Gα-RGS protein recognition (*8*, *12*). Strikingly, none of the mutations in $G\alpha_q$ that affected GRK2 binding interfered with the binding of RGS proteins (Fig. 3C). Therefore, $G\alpha_q$ binds the GRK2 RH domain using a surface distinct from that used for binding RGS proteins. Indeed, when RGS4 is modeled in complex with $G\alpha_{i/q}$, there is no obvious steric overlap between RGS4 and GRK2 (Fig. 4A), which implies that $G\alpha_q$ could bind two different RH domains at the same time: one as an effector (GRK2) and the other as a GAP (RGS protein). This model also predicts that the α-helical domain of $G\alpha_q$ will form substantial contacts with RGS4 (and presumably RGS2)

that are not possible in $G\alpha_i$ or $G\alpha_t$ owing to substitutions in αA and differences in the structure of the αB-αC loop (Fig. 4B). This novel interaction may help dictate the relative specificity of RGS4 and RGS2 for $G\alpha_q$ (*41*).

Together with the $G\alpha_s$–adenylyl cyclase, $G\alpha_t$-PDEγ-RGS9, and $G\alpha_{13}$-p115RhoGEF complexes (*7*, *8*, *10*), the $G\alpha_{i/q}$-GRK2-Gβγ structure completes a survey of effector complexes representing the four Gα protein subfamilies (Fig. 4B). Comparison of these structures demonstrates that structurally diverse effectors recognize a highly localized region on each Gα subunit in a manner that does not necessarily exclude the binding of GAP domains (Figs. 3B and 4C). In each case, solvent-exposed hydrophobic side chains from the effector dock into a nearly invariant pocket formed between the N termini of the switch II (α2) and α3 helices of Gα (Fig. 3B; Fig. 4, B and C). Additional specificity-determining contacts are made with residues at the C-terminal ends of these helices and within the α2-β4 and α3-β5 loops (Fig. 3B). With the exception of the α3-β5 loop in $G\alpha_s$, the tertiary structures of the effector interacting regions are well conserved (Fig. 4B), which implies that effector specificity in most Gα subunits is dictated by primary sequence and, at least in some cases, differences in electrostatic potential (fig. S4).

The physiological consequence and/or necessity of GRK2 binding both $G\alpha_q$ and Gβγ is not known, but the nanomolar affinity of these interactions (*25*, *42*, *43*) and the expected close proximity of these proteins to each other while associated with the membrane suggest that a $G\alpha_q$-GRK2-Gβγ complex can form soon after a G_q-coupled receptor is activated. Simultaneous engagement of Gα and Gβγ is a characteristic shared among GRK2 and classic effectors like adenylyl cyclase and PLC-β. This, along with the observed effector-like interaction between GRK2 and $G\alpha_q$ and the fact that heptahelical receptors directly stimulate the kinase activity of GRK2 (*22*), invokes the question of whether GRK2 can instigate its own signaling cascade. Potential downstream targets include insulin receptor substrate–1 (IRS-1) (*44*) and the cytoskeletal regulator ezrin (*45*), which can be phosphorylated by GRK2 in response to activation of G_q-coupled receptors.

An increasing body of evidence suggests that GPCR signaling systems can function as preassembled complexes, which should allow for efficient transmission and desensitization of extracellular signals (*19*). The $G\alpha_{i/q}$-GRK2-Gβγ structure strongly supports this hypothesis, at least in the case of G_q-coupled receptors, with GRK2 harboring at least one additional protein-binding site for an activated receptor. The potential coassembly of this complex with RGS proteins like RGS4 and RGS2 (Fig. 4A) is intriguing in light of their reported association with receptor complexes (*46*–*49*). Defining the molecular basis for the interactions among GPCRs, RGS proteins, heterotrimeric G proteins, and GRK2 will be the focus of future studies.

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Supporting Online Material

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Materials and Methods
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Figs. S1 to S4
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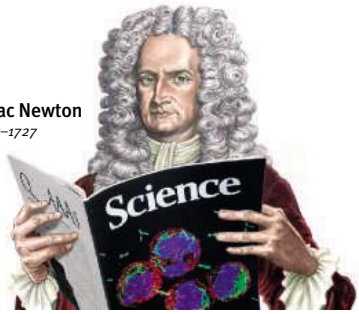

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POSITIONS OPEN

CHAIR, DEPARTMENT OF BIOLOGY
The University of Akron

The Department of Biology invites applications for a departmental Chair beginning August 28, 2006. Salary is competitive and significant research support will be provided. The successful candidate must have a distinguished record which would merit appointment at the rank of Full Professor with tenure. Applicants should have a commitment to promoting research, teaching and service at both undergraduate and graduate levels, and should have excellent interpersonal skills. Duties will include supervising support staff, instructors and faculty and being an advocate for biology's interests to the College, University and community.

Candidates who can articulate and implement plans that allow faculty to continue their recent gains in research productivity are preferred. Primary among such skills must be the ability to spearhead implementation of a new Ph.D. program in integrated bioscience. This program is designed to increase collaborative research between biology and other sciences, both at the University of Akron and regionally. Candidates should be both conversant across a broad spectrum of biological disciplines and have the ability to facilitate interactions with other departments. The Department is also strongly committed to teaching excellence and innovation, at both the graduate and undergraduate levels. Candidate must be able to lead our department in its quest for excellence in service to university, profession and community. Ability to cultivate new fundraising opportunities for the department and the college required.

The Department of Biology has 20 full-time faculty enrolling 600 majors. Faculty members have active, extramurally-funded research programs that span the range from molecular biology to community ecology. Extramural research funding to Biology faculty has more than doubled in the last ten years, with total funding exceeding $1,000,000 annually. The Biology Department is housed in a 38,000 square foot building, with a new 45,000 square foot building planned to begin construction in 2006. The Department oversees an animal research facility and a field station located on a nearby nature preserve. For additional information about the Biology Department visit **website: http://www3.uakron.edu/biology/.**

Review of applications will begin January 15, 2006. Applicants should submit curriculum vitae, statements on administrative philosophy, research and teaching, copies of recent publications, and three letters of recommendation to: **Chair, Biology Chair Search, Department of Biology, The University of Akron, Akron, OH 44325-3908.** *The University of Akron is committed to a policy of Equal Employment Opportunity and to the principles of Affirmative Action in accordance with state and federal laws.*

Wheaton College, Wheaton, Illinois, seeks candidates for an **ASSISTANT OR ASSOCIATE PROFESSOR** tenure-track position in physics to begin in August, 2006. Field of expertise is open within the general area of experimental physics; special consideration will be given to abilities in leadership, teaching, and promise for sustained scholarship in an undergraduate liberal arts college. The ideal candidate will be able to serve as departmental Chair. Two national laboratories are within twenty miles of campus.

Review of applications will begin December 15, 2005, and continue until the position is filled. Applicants should send curriculum vitae and a description of the applicant's teaching philosophy and research interests to: **Dr. Dorothy F. Chappell, Dean of Natural and Social Sciences, Wheaton College, Wheaton, IL 60187.** Application materials will be sent to eligible candidates.

Wheaton College is an evangelical protestant Christian liberal arts college whose faculty members affirm a Statement of Faith and the moral and lifestyle expectations of our Community Covenant. The College complies with federal and state guidelines of nondiscrimination in employment; women and minorities are encouraged to apply.

POSITIONS OPEN

TENURE-TRACK FACULTY POSITION
Department of Biochemistry and Molecular Biology/ Center for Computational Biology and Bioinformatics
Indiana University School of Medicine

Faculty position at any rank is available in a newly formed Center for Computational Biology and Bioinformatics in the Department of Biochemistry and Molecular Biology at the Indiana University School of Medicine. The School has embarked on a major initiative to enhance computational and bioinformatics research. The Center is part of the Indiana Genomics Initiative (INGEN; **website: http://www.ingen.iu.edu/**), made possible by a grant from the Lilly Endowment. Areas of interest include simulations of protein-ligand interactions, virtual ligand screening and structure-based drug design, protein-protein interactions, modeling of protein interaction networks, and protein folding. Candidates will be evaluated on the following criteria: (1) ability to develop and direct an internationally recognized and externally funded research program with direct relevance to computational biology or bioinformatics, (2) interest in participating in collaborative research teams as evidenced by prior research collaborations, especially with experimental biologists, (3) interest in assigning function to, and determining the interactions among, the functional entities emerging from genomic data, especially by novel and insightful methods; (4) ability to train students and postdoctoral fellows and participate in graduate and medical student teaching. Competitive space and startup funding are available. Application and reference letters addressing the four criteria listed above should be sent to: **Dr. Keith Dunker, Director, Center for Computational Biology and Bioinformatics, 714 N. Senate Avenue, Suite 250, Indianapolis, Indiana 46202** or via **e-mail: apply@compbio.iupui.edu.**

Indiana University is an Equal Employment Opportunity/ Affirmative Action Employer. Minorites, females, and persons with disabilities are encouraged to apply.

DEPARTMENT HEAD POSITION
Purdue University Calumet
Department of Biological Sciences

The Department of Biological Sciences at Purdue University Calumet invites applications for the position of Department Head, to begin in July 2006. Candidates with the rank of associate or full professor are invited to apply. Candidates must have a Ph.D. in biological science as well as a strong record of teaching, and externally funded research. We seek an energetic person with demonstrated leadership who can lead the department in continued program development, excellence in teaching and scholarly activity, and growth in external funding. Purdue University Calumet, the Chicago-area campus of the Purdue University system, is a M.S. comprehensive university with a current enrollment of 9,200 students. The Department consists of nine full-time faculty and has approximately 350 undergraduate majors and 30 M.S. graduate students. The department offers quality programs in molecular/genetics, microbiology, cell/neurobiology, and ecology and has state-of-the-art facilities and equipment for research and teaching.

This is a twelve-month position with a competitive salary and compensation. Application review will start January 23, 2006, and continue until the position is filled. Interested applicants should submit curriculum vitae and statements of philosophy on teaching, research/scholarship and administration, along with contact information for three references to:

Head Search
Department of Biological Sciences
Purdue University Calumet
2200 169th Street, Hammond, IN 46323
E-mail: biosearch@calumet.purdue.edu.

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UNIVERSITY of CALIFORNIA Riverside College of Natural and Agricultural Sciences

Faculty Position Announcements

Plant Evolutionary Genomics

The College of Natural and Agricultural Sciences invites applications for a tenure track 9-month academic position at the assistant level in the area of Plant Evolutionary Genomics. Possible areas of specialization include molecular population genetics, molecular evolution, genome evolution, evolutionary genetics, and comparative genomics of plants. The research could focus on molecular analysis of adaptations, the nature and rate of evolutionary change in genes and genomes, molecular genetic analysis of plant speciation or plant domestication, hybridization, evolution of invasiveness and other similar topics.

Applicants interested in theory, modeling and data mining, as well as those conducting experimental, laboratory or natural population studies will be considered. The candidate will hold a faculty position in the academic department of his or her discipline as well as a joint appointment in the Agricultural Experiment Station. The successful candidate will be expected to establish and maintain a vigorous, innovative research program, and have a strong commitment to excellence in teaching at the undergraduate and graduate levels.

Chair, Plant Evolutionary Genomics Search Committee
Department of Botany and Plant Sciences
University of California, Riverside, Riverside, CA 92521-0124
bpssearch@ucr.edu FAX (951) 827-4619

Conservation Ecology/Biology

The College of Natural and Agricultural Sciences invites applications for a tenure track 9-month academic position at the assistant professor rank beginning Fall 2006. A Ph.D. in Conservation Ecology/Biology or related field and at least one year of postdoctoral research experience are required. Applicants are expected to develop a fundamental research program in Conservation Ecology/Biology. Applicants with an emphasis in community to landscape or regional ecology are especially encouraged. The position is open to any area of Conservation Biology, but particular emphasis is placed on topic areas focusing on multiple species interactions examined over community to landscape or regional scales.

Potential collaborators include over one hundred faculty, ranging from conservation geneticists and population biologists to economists and anthropologists. Opportunities also include collaborations within a variety of research centers within the College (**http://www.cnas.ucr.edu/centers/index.html**). The successful candidate will hold a faculty appointment in the academic department of her or his discipline. Contributions to teaching at the undergraduate and graduate levels are expected, and there are a variety of departmental and interdepartmental programs that provide opportunities for graduate training.

Chair, Conservation Ecology/Biology Search Committee
Department of Biology
University of California, Riverside, CA 92521-0334
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Evolutionary Ecology

The Department of Biology invites applications for a tenure track 9-month academic position in the general area of evolutionary ecology. We are interested in individuals who are strongly quantitative, working to link data with theory. Taxonomic focus and system are open, but preference will be given to candidates who work in the areas of coevolution, metapopulation dynamics or interspecies interactions, and whose research complements some aspect of existing college strengths in ecology, evolution, physiology, behavior, paleobiology and genetics. The successful candidate will be expected to establish and maintain a vigorous research, and have a strong commitment to excellence in teaching by participating in the graduate program in Evolution, Ecology and Organismal Biology, and in the undergraduate programs in Biology and Biological Sciences. There will also be an opportunity to participate in other programs, such as the Graduate Program in Genetics, Genomics, and Bioinformatics or to be affiliated with the Center for Conservation Biology.

Chair, Evolutionary Ecology Search Committee
Department of Biology
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biochair@ucr.edu FAX (951) 827-4286

The review of applications for the above positions will begin on **January 20, 2006**, with appointment as early as July 1, 2006. Applicants must hold a Ph.D. and postdoctoral experience of 1-3 years is essential for candidates at the assistant level. Salary is commensurate with education and experience. Applications will be accepted until the positions are filled. Interested individuals should submit the following: (1) a curriculum vitae, (2) a statement of research and teaching interests, (3) samples of relevant publications, and (4) have three letters of recommendation sent to the respective committee for each position. For additional information about the UCR campus, the College of Natural and Agricultural Science and these research areas, please visit our web sites at **www.ucr.edu**, **www.cnas.ucr.edu**, **www.plantbiology.ucr.edu**, **www.biology.ucr.edu** and **www.ccb.ucr.edu**.

Entomology

Assistant Professor in the area of Insect Systematics, University of California, Riverside. Position available July 1, 2006, 9-month, 50% Instruction and Research, 50% Agriculture Experiment Station. Appointment level and salary commensurate with experience. Ph. D. in Entomology or related discipline required. The successful candidate must have strong training and experience with modern methods applicable to systematic entomology. Preference will be given to candidates with an interest in systematics of groups considered important to applied entomology. A program of research should be in accordance with Department and College strengths in agricultural entomology, biological control, evolution, or conservation biology. It is expected that the successful individual will build a strong extramurally funded independent research program, develop cooperative research with other faculty in the Department and College, and participate in the Department's teaching program. Send curriculum vitae, transcripts, statement of research interests, reprints, manuscripts in press, and the names and addresses of five referees by **January 20, 2006** to: **Dr. Richard Stouthamer, Search Committee Chair, Department of Entomology, University of California, 3401 Watkins Dr., Riverside, CA 92521**; e-mail: **richard.stouthamer@ucr.edu**; phone **(951)-827-2422**. This position will remain opened until filled. Information about the Entomology Department and an expanded position description can be found on the website: **http://www.entomology.ucr.edu**.

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National Institute of General Medical Sciences
National Institutes of Health

The National Institute of General Medical Sciences (NIGMS) in Bethesda, MD is seeking applications from outstanding candidates for a Health Scientist Administrator (HSA) position in the Pharmacological and Physiological Sciences Branch within the Pharmacology, Physiology, and Biological Chemistry Division. The recruiting branch currently supports research and training into understanding the basis of traumatic and burn injury and the perioperative period, the molecular basis of action of anesthetics, the mechanisms of and genetics underlying the actions of therapeutic drugs, and the development of predictive preclinical toxicology approaches.

The individual hired will be responsible for applying his/her clinical and research expertise to manage and develop research and training grants in NIGMS' broad areas of basic studies in pharmacological and physiological sciences, and to foster the translation of results from fundamental research areas into clinical studies. The person should have experience gained in a medical research institution and understand how research is conducted with human subjects or patients in a clinical setting. A background in at least one of the following areas is preferred: trauma, injury and recovery, or clinical pharmacology, or immune system biology, or alternatively in a cross-cutting area such as studies of the role of inflammation in the disease process or of molecular/cellular signaling in these systems. Experience in modern methods of genome or proteome analysis would also be desirable.

Applicants must possess an MD and/or PhD plus scientific knowledge in the fields of pharmacology, physiology, immunology, systems biology, medicine, or related fields. Applicants must be familiar with both clinical and laboratory approaches in his/her own field(s) of expertise. Experience in the NIH peer review and grant award process would be beneficial. Salary will be commensurate with qualifications, may include a physician's comparability allowance, and will have a full package of benefits. Detailed vacancy announcements **NIGMS-05-100271** and **NIGMS-05-100881** with the qualifications and application procedures are available at the NIGMS web page at **http://www.nigms.nih.gov/about/job_vacancies.html**. Questions about application procedures may be directed to **Erin Bandak at 301-594-2324**. Applications must be received by **January 4, 2006**.

Branch Chief Positions
National Human Genome Research Institute

The National Human Genome Research Institute (NHGRI) of the National Institutes of Health (NIH) is seeking one or two dynamic and experienced senior investigators to serve as Branch Chiefs in its Intramural Program. The Division of Intramural Research at NHGRI is a world-class, highly collegial research environment, where basic and clinical research is performed in a highly integrative fashion in the broad areas of genetics, genomics, diagnostics, and therapeutics.

The successful candidate(s) will have significant leadership responsibilities, involving the oversight of an existing cadre of investigators with research programs in human genetics, developmental genetics, chromosome biology, gene therapy, immunology, neuroscience, and stem cell biology as well as leading future recruitment efforts. A vision for crafting cutting-edge research programs that advance the frontiers of genetics and genomics will be key. In addition to superlative scholarship, the successful candidates must have well-honed administrative skills to lead a large and diverse research program.

These fully funded, tenured positions will include appropriate start-up allowances, an ongoing commitment of clinical and laboratory resources, and positions for support staff and trainees. In addition to the resources of the NIH Clinical Research Center, there will be full access to NHGRI core facilities. Candidates must have an M.D., Ph.D., or equivalent degree, as well as advanced training and demonstrated accomplishment in genetic and/or genomic research.

Interested applicants should submit their curriculum vitae, a three-page description of their research program, and three letters of recommendation through our online application system, at http://research.nhgri.nih.gov/apply.

The closing date for these positions is March 1, 2006.

For more information about the NHGRI Intramural Program, please see http://www.genome.gov/DIR
Specific questions regarding these positions may be directed to Dr. Andy Baxevanis (Search Chair) at andy@nhgri.nih.gov or by fax (301-480-2634).

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Tenured/Tenure-Track/Senior Scientist Positions
National Eye Institute

The National Eye Institute (NEI) at the National Institutes of Health is seeking outstanding and creative scientists for several Tenured, Tenure-Track and Senior Scientist positions as part of a new multidisciplinary initiative for therapy of retinal genetic neurodegenerations. The program will be located within the Institute's Division of Intramural Research NEI, National Institutes of Health (NIH), Department of Health and Human Services (DHHS). These positions offer an opportunity to participate in an organization dedicated to uncovering new scientific knowledge, both basic and clinical, and ensuring the translation of that knowledge to the treatment of ocular diseases.

Investigators chosen for this Program will have access to clinical resources and research programs of the NEI as well as the intellectual and technical resources of the entire NIH. Investigators are expected to provide scientific leadership and expertise in one or more disciplines that include genetics, gene therapy, molecular biology, cellular biology, physiology, developmental neurobiology, or animal studies as they relate to the design and conduct of pre-clinical and clinical therapeutic retinal genetic disease research. The basic science components will interface with the existing clinical expertise within NEI on ophthalmic genetic diseases.

This will be a comprehensive program to move into human therapy. The following approaches are pertinent to this effort: molecular genetic analysis of fundamental questions in retinal disease; biochemistry of transcriptional regulation; genetic basis of cellular differentiation and pattern formation in a multicellular tissue; molecular and cellular mechanisms of retinal development and their role in the progression and treatment of retinal degenerative diseases; molecular basis of cell-cell interactions that regulate retinal neurogenesis and neuronal specificity during development and regeneration; pre-clinical animal models for retinal degenerative diseases; pharmacogenetics; cell-based therapies; molecular control of stem cell neurobiology and self-renewal; neural remodeling in retinal degenerative diseases.

Salary is commensurate with research experience and accomplishments. A full Federal package of benefits is available (including retirement, health, life and long term care insurance, Thrift Savings Plan etc).

Applicants should submit curriculum vitae, bibliography, copies of three major publications, a summary of research accomplishments, a brief statement of future research goals, and three reference letters to: **Sheila Ayala, Intramural Administrative Specialist, Office of the Scientific Director, National Eye Institute, 31 Center Drive, Building 31, Room 6A22, Bethesda, MD 20892, Tel: 301-451-6763, Email: sayala@nei.nih.gov.**

This position will be open until filled.

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We are seeking a qualified scientist, with doctorate level training and independent research and supervisory experience in cell biology to lead a team of Scientific Review Administrators (SRAs) to help shape the future of scientific review. This position is Chief of the Cell Biology (CB) Integrated Review Group (IRG). The CB IRG is responsible for the initial administrative and scientific review of NIH research grant and training applications in all areas of cell biology. The incumbent will be responsible for supervising SRAs and for handling a partial review load. An M.D. or Ph.D. degree (or have equivalent training and experience) is required. For additional information on the IRG please see our web site, at: **http://cms.csr.nih.gov/PeerReviewMeetings/CSRIRGDescription/CBIRG/**

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For additional information on this position, and for instructions on submitting your application, please see our website, at: **http://www.hhs.gov/careers/** and it will take you to **www.usajobs.opm.gov** The closing date for this position is **January 12, 2006.**

ALLERGIC INFLAMMATION
National Institute of Allergy and Infectious Diseases

A Postdoctoral Fellowship position is open in the Allergic Inflammation Section, LAD/NIAID/NIH to study the in vivo mechanisms of allergic inflammation/asthma using animal models. Approaches include physiology, as well as cellular and molecular biology and imaging techniques, to determine changes that occur during the allergic cascade using newly developed knockout and transgenic mouse lines.

The preferred candidate will have an MD, MD/PhD, or PhD degree in biological sciences and a recent peer-reviewed publication record. To apply, send cover letter, curriculum vitae, and the names with contact details (e-mail preferred) of three (3) references by **12/15/05** to:

Andrea Keane-Myers, Ph.D.
AIS/LAD/NIAID/NIH
Twinbrook II, Room 125
12441 Parklawn Drive,
Rockville, MD 20892-8180, USA
E-mail akeane@niaid.nih.gov

The **European Molecular Biology Laboratory**, EMBL an international research organisation, is searching for **Group Leaders** to lead independent research groups. EMBL offers a highly collaborative, uniquely international culture. It fosters top quality, interdisciplinary research by promoting a vibrant environment consisting of young independent research groups with access to outstanding graduate students and postdoctoral fellows.

CELL BIOLOGY AND BIOPHYSICS UNIT
HEIDELBERG, GERMANY **05/124/CBB**

has developed an original interdisciplinary approach to cell biology where physicists work closely together with cell biologists, geneticists, molecular biologists and scientists developing new sophisticated dynamic microscopy methods. This unit is seeking innovative candidates in the broad area of regulatory networks with emphasis on cell motility and morphogenesis and the roles of microfilaments and signalling events in such processes.

DEVELOPMENTAL BIOLOGY UNIT
HEIDELBERG, GERMANY **05/124/DB**

applies a wide range of modern technologies to diverse problems of whole organism biology. Groups in the unit use a diverse range of model organisms including fly, fish, annelid and mouse. For this position, we particularly encourage applicants using the mouse as a model system.

EUROPEAN BIOINFORMATICS INSTITUTE (EBI)
HINXTON, UK **05/121/EBI**

is the European centre for collecting, archiving and distributing biomolecular data. We wish to recruit a young scientist keen to develop new bioinformatics methods to exploit the flood of biological data. We are particularly interested in moving towards systems biology with the areas of comparative genomics; metabolomic/chemical biology; and human diversity in the genetics of multifactorial disease, although any outstanding candidate would be considered.

EMBL GRENOBLE OUTSTATION
GRENOBLE, FRANCE **05/124/GR**

focuses on the structural molecular biology of complexes involved in eukaryotic cellular processes. We seek a dynamic, independent group leader with demonstrated excellence in structural, molecular or cell biology on complexes and a desire to work in a multidisciplinary structural biology environment. We encourage applicants working on cellular aspects of structural biology using techniques such as characterization of complexes in cells by TAP-tagging, RNAi or in vivo imaging. However candidates using traditional methods are also welcome.

For further details and more comprehensive job descriptions please visit: **www.embl.org**

To apply, please email a CV, three references and a concise description of research interests and future plans, quoting the corresponding ref. no. in the subject line, to: **application@embl.de**

GROUP LEADERS

EMBL

THE STATE UNIVERSITY OF NEW JERSEY
RUTGERS

Professor and Chair of Nutritional Sciences

The Department of Nutritional Sciences of Rutgers University seeks a renowned scientist to chair and build the department to a level of international prominence. To make a significant impact on human health, Rutgers has targeted nutrition and its health consequences as a principal area for programmatic growth. The successful candidate will take a leadership role through the recruitment of new faculty, the development of major new facilities, and the fostering of multidisciplinary research and training programs. Nutritional Sciences is located at Cook College, Rutgers' school of food and environmental sciences and site of its Land Grant mission and activities, and there are ongoing collaborations with other Cook departments including Animal Sciences, Plant Biology and Pathology, Food Science, and Biotechnology. Nutritional Sciences is also part of a vibrant life sciences research community at Rutgers University, including major programs in structural biology, molecular, cellular and developmental biology, neuroscience, the Stem Cell Institute of New Jersey, the Cancer Institute of New Jersey, the Center for Advanced Biotechnology and Medicine, the Center of Alcohol Studies, the Environmental and Occupational Health Sciences Institute, the Human Genetics Institute, The School of Public Health, and the Robert Wood Johnson Medical School. The campus is located in central New Jersey, close to New York City, Philadelphia, beaches, and countryside.

The **Nutritional Sciences Department** has 17 full-time faculty members involved in undergraduate, graduate, and outreach programs. The faculty's research areas include lipid metabolism, calcium and bone development, energy expenditure and obesity, amino acid metabolism, child nutrition, community nutrition, and health promotion (**http://nutrition.rutgers.edu/**). The successful candidate will strengthen and extend the department's research areas in health and clinical fields involving the etiology, prevention, and treatment of nutrition-related diseases, including obesity, diabetes, CVD, cancer and osteoporosis. The successful candidate will direct the Nutritional Sciences Department, direct the department's research and educational programs, and oversee faculty mentoring.

Qualifications: The successful candidate must have a Ph.D. and/or M.D. or their equivalent and a record of distinguished research and scientific leadership. The successful candidate should have strong interpersonal skills and a sustained record of peer-reviewed publications and research funding. The successful candidate will be provided with a highly competitive salary, significant start-up support and laboratory space, and substantial administrative support. This is a tenure track position.

Inquiries and nominations should go to **Dr. Michael A. Gallo, Professor, Environmental and Occupational Medicine, Robert Wood Johnson Medical School, 170 Frelinghuysen Rd., Piscataway, NJ, 08854 (magallo@eohsi.rutgers.edu)**.

A letter of application, curriculum vitae, names of four or more professional references, and a statement of research and leadership objectives should be sent by electronic or regular mail to **Ms. Phyllis Lepucki, Rm 004, Martin Hall, 88 Lipman Drive, Cook College, Rutgers, The State University of New Jersey, New Brunswick, NJ 08901 (lepucki@aesop.rutgers.edu)**. A review of applications will begin on **February 15, 2006** and continue until a suitable candidate is identified. Starting date is negotiable, on or after July 1, 2006.

Rutgers University is an Equal Opportunity/Affirmative Action Employer.

IN 2006

CNRS IS RECRUITING

MORE THAN 410 TENURED RESEARCHERS IN ALL SCIENTIFIC FIELDS*

*MATHEMATICS; PHYSICS; NUCLEAR AND HIGH-ENERGY PHYSICS; CHEMISTRY; ENGINEERING SCIENCES; COMMUNICATION AND INFORMATION TECHNOLOGY AND SCIENCES; EARTH SCIENCES AND ASTRONOMY; ENVIRONMENTAL SCIENCES; LIFE SCIENCES; HUMANITIES AND SOCIAL SCIENCES.

This recruitment campaign is open to junior and senior researchers from all over the world. One of the major objectives of this campaign is to encourage international scientists to apply to CNRS.

CNRS researchers work in an enriching scientific environment:
› numerous large-scale facilities
› highly-skilled technical support
› multiple networks throughout Europe and across disciplines
› access to university research and teaching
› lab-to-lab and international mobility

At CNRS, a long-term vision of excellence in basic research provides a solid foundation for the latest technological research. Successful candidates from the CNRS competitive entry process benefit from the dynamics, stability and stimulation of belonging to a major research organization.

Application deadline: January 16th 2006.

www.cnrs.fr

CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

Department Head
Department of Biochemistry and Molecular Biology
Franklin College of Arts and Sciences
University of Georgia

The University of Georgia is seeking an established scientist with creative vision to lead the Department of Biochemistry & Molecular Biology [http://www.bmb.uga.edu/home/]. With over 30 faculty members, the internationally recognized department has research strengths in several areas, including glycobiology, structural biology, bioinformatics, microbial genomics, enzyme mechanisms, and molecular/cellular biology. This search is coincident with a dramatic expansion of research programs in interdisciplinary biomedical and health sciences at UGA, the establishment of a new College of Public Health, the development of state-of-the-art biohazard containment facilities, and increasing emphasis on quantitative approaches to biological and medical problems [see **http://www.ovpr.uga.edu/facultypositions/**].

Candidates should have an outstanding record of academic accomplishments and funding, as well as proven leadership and administrative skills. Send applications and nominations electronically to **Dr. Wyatt W. Anderson, Chair of the Search Committee, chairheadsearch@bmb.uga.edu**. Applicants should submit a cover letter summarizing their qualifications and vision, together with complete curriculum vitae. For full consideration, applications must be received by **January 5, 2006**.

The University of Georgia is an Equal Opportunity/Affirmative Action Employer.

UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN

School of Molecular & Cellular Biology and College of Medicine

The School of Molecular and Cellular Biology (http://www.life.uiuc.edu/mcb/) and the College of Medicine (http://www.med.uiuc.edu/) at the University of Illinois at Urbana-Champaign invite applications for multiple tenure track faculty positions as described below. The starting date for these positions is August 16, 2006. These positions offer the opportunity to join a rapidly growing group of outstanding biological scientists on a campus that provides a highly interactive, interdisciplinary research environment and state-of-the-art research support facilities. The University of Illinois at Urbana-Champaign has added significant faculty strength in the biological sciences over the last five years and we anticipate additional hires in these and related areas each year for the next several years. Each of these positions offers excellent laboratory facilities, substantial start-up funds, and the opportunity to work with outstanding graduate students.

The UIUC campus offers a wide range of state-of-the-art research support facilities, including mass spectrometry, NMR, X-ray crystallography, micro- and nanoscale fabrication and analysis, the Roy J. Carver Biotechnology Center, the W. M. Keck Center for Comparative and Functional Genomics as well as facilities for proteomics, metabolomics, immunological resources and flow cytometry. Superb resources for computational biology are available on campus at the National Center for Supercomputing Applications and the NIH Resource for Macromolecular Modeling and Bioinformatics. The Institute for Genomic Biology (http://www.igb.uiuc.edu/), a new 186,000 square foot facility devoted to biological research, will open in 2006.

Salaries for these positions are commensurate with experience and are competitive. Urbana-Champaign offers the residential advantages of a medium-sized university city, excellent cultural opportunities, and easy access to Chicago, St. Louis, and Indianapolis.

Biochemistry – Assistant Professor

We invite applications for a full-time, tenure-track faculty position at the Assistant Professor level in the Department of Biochemistry. We are seeking outstanding candidates whose research investigates the molecular basis of biological or biomedical processes. Our priority is for candidates interested in membrane structure/function, but we will consider strong applicants in all areas of biochemistry. Appointment at the Assistant Professor level requires a doctoral degree, postdoctoral experience, and evidence of outstanding research potential and the ability to develop a vigorous, independently-funded research program. In exceptional cases, appointment at more senior levels may be considered, and would require strong evidence of outstanding research accomplishments, including extramural funding and international recognition. Appointees will be expected to share in the Department's responsibilities for teaching undergraduate and graduate courses in biochemistry.

Bioinformatics –Rank Open

The Department of Microbiology in conjunction with the Institute for Genomic Biology solicits applications for an open rank, full-time tenure-track position in bioinformatics and computational biology. This position requires a doctoral degree, postdoctoral experience, and evidence of outstanding research potential. The individual sought for this position should be able to develop a cutting-edge research program involving computational analysis of microbial genomes. Possible research areas include the development and application of new computational approaches for genome annotation, for the identification of functions for unknown proteins, for reconstructing metabolic pathways, and for building computational models for metabolic and regulatory networks. Candidates with expertise in generating global physiomic profiles by integrating data from genomic, proteomic, and metabolomic studies or in the areas of pharmacogenomics, toxicogenomics, or pharmacogenetics will also be considered. The successful candidate will be housed in the new Institute for Genomic Biology. When this state-of-the-art facility opens in Fall, 2006 it is expected to house approximately 400 researchers across a variety of biological disciplines, providing ample opportunities for collaboration. This position is part of a campus-wide initiative in bioinformatics involving multiple hires in the past year and active participation by the National Center for Supercomputing Applications. Appropriately qualified applicants may also seek affiliation with the Department of Computer Sciences.

Cell Biology – Rank Open

One or more positions are available in the Department of Cell and Developmental Biology (http://www.life.uiuc.edu/cdb/) for outstanding candidates whose research addresses fundamental questions of modern cell biology. Applications for full-time positions at the Assistant, Associate and Full Professor levels will be considered, and highly qualified scientists at these levels are encouraged to apply. Appointment at the Assistant Professor level requires a Ph.D. and/or M.D. degree, postdoctoral experience, and evidence of outstanding research potential. Appointees at this level will be expected to develop a vigorous, independently funded research program. Appointment at the higher levels requires evidence of outstanding research accomplishments. Applicants at all levels will be responsible for undergraduate, graduate or medical cell biology teaching.

Pharmacology – Assistant Professor

The Department of Pharmacology in the College of Medicine and the School of Molecular and Cellular Biology invite applications for a full-time tenure-track faculty position at the Assistant Professor level. A Ph.D. and/or M.D. degree and postdoctoral experience are required for appointment to this position. Applicants should be qualified to teach basic principles of pharmacology to second year medical students in the College of Medicine. Appointees will be expected to develop a vigorous, independently-funded research program that addresses contemporary questions in biochemistry, cell and molecular biology, or physiology. Applicants may also be considered for an appointment in Chemical Biology in the School of Chemical Sciences (http://www.scs.uiuc.edu/), if appropriate.

Applications should clearly indicate the position(s) applied for and should be submitted to: School of Molecular and Cellular Biology Search, University of Illinois at Urbana-Champaign, 393 Morrill Hall, 505 S. Goodwin Ave., Urbana, IL 61801. The application must include a curriculum vitae with a complete list of publications, a concise summary of past research accomplishments, and future research plans. Please arrange to have no fewer than three letters of recommendation sent to the same address.

Electronic submissions as pdf or Microsoft Word files are encouraged and should be sent to mcbsearch06@life.uiuc.edu. To ensure full consideration, applications must be received by January 3, 2006. Applicants may be interviewed before the closing date; however, no hiring decision will be made until after that date.

The University of Illinois at Urbana-Champaign is an Affirmative Action, Equal Opportunity Employer.

FACULTY POSITION IN BIOMATERIALS AND NANOTECHNOLOGY FOR DRUG DELIVERY

UNIVERSITY OF CALIFORNIA, IRVINE

The Program in Pharmaceutical Sciences within the College of Health Sciences, in collaboration with the Department of Chemical Engineering and Materials Science in the Henry Samueli School of Engineering, seeks applicants for a tenure-track position at the **ASSISTANT PROFESSOR** level to begin July 1, 2006. Applicants should hold a Ph.D. or equivalent degree. The Department and Program particularly encourage applicants who are interested in research in biomaterials and nanotechnology as applied to drug discovery and drug delivery. The successful candidate must demonstrate outstanding potential, and is expected to establish a vigorous research program and participate in undergraduate and graduate teaching. In addition, the successful candidate will have an opportunity to play a significant role in the development of the newly established Program in Pharmaceutical Sciences.

Applicants should submit a description of their research accomplishments including future research and teaching plans, a Curriculum Vitae, and letters from at least three references. To submit your application to our on-line recruitment program (preferred), you will find the URL link at our website at: **http://www.eng.uci.edu/jobs/faculty**. You can also send your application to: **Chair, Drug Delivery Search Committee, Department of Chemical Engineering and Materials Science, ET 916, University of California, Irvine CA 92697-2575**.

DEADLINE FOR RECEIPT OF APPLICATIONS: Review of applications will begin **January 15, 2006** and the recruitment will remain open until a suitable candidate has been hired.

The University of California has an active career partner program and an NSF ADVANCE Program in Gender Equity and is an Equal Opportunity Employer committed to excellence through diversity.

ASSISTANT, ASSOCIATE, FULL PROFESSOR IN ENVIRONMENTAL, RESOURCE, OR ECOLOGICAL ECONOMICS

The Global Institute of Sustainability invites applications for up to three faculty positions in Environmental, Resource, or Ecological Economics. The appointments are in support of an interdisciplinary academic program in sustainability science to be implemented by a planned School of Sustainability Science, in which economics of the environment are part of the core. Appointments and tenure arrangements may be either solely in the School of Sustainability Science, or may be shared or associated with the Department of Economics, the School of Global Studies, the School of Human Evolution and Social Change, the School of Life Sciences, or other appropriate department.

The successful candidate will teach graduate and undergraduate classes, conduct interdisciplinary research and publish in area of specialization, and perform appropriate university, professional, and community service.

Required qualifications are: an earned doctorate at the time of appointment in an area of economics or a closely related field with specialization in environmental, resource, or ecological economics; demonstrated strong record of scholarly achievement and publications in appropriate journals appropriate to rank; demonstrated strong communication skills; demonstrated experience working effectively in an interdisciplinary setting appropriate to rank; demonstrated record of excellence in education appropriate to rank, particularly at the doctoral level; and demonstrated evidence of or potential to secure research funding. For senior appointments, candidates must be qualified for a tenured faculty position at the appropriate rank within the relevant School.

Desired qualifications are demonstrated experience in one of the following areas: urban environmental issues, water resources, sustainable exploitation of ecosystem services; and applied research interests at the international level, including in developing countries.

Application deadline is **January 31, 2006**; if not filled, every two weeks thereafter until search is closed. Applicants must send a letter of interest, current curriculum vitae, and the names, addresses, phone numbers, and email addresses of three references, to: **Karen Gronberg, School Faculty Search, Global Institute of Sustainability, Arizona State University, PO Box 873211, Tempe, AZ 85287-3211** or to **gronberg@asu.edu**. A background check is required for employment.

AA/EOE

Institute of Molecular and Cell Biology
A*STAR

Postdoctoral Fellows Opportunities

The Institute of Molecular and Cell Biology, Singapore, which carries out basic and applied research in selected areas of molecular and cell biology, developmental biology, cancer, structural biology, translational research and infectious diseases, has excellent opportunities for postdoctoral fellows in the following fields as listed in the table below. Salaries and benefits are highly competitive.

Applicants should post, fax or e-mail their c.v.'s, stating research interests and the names of three referees, to: The Administrative Office, Institute of Molecular and Cell Biology, 61 Biopolis Drive, Proteos, Singapore 138673. Fax: Singapore (+65) 6779-1117. E-mail: recruit@imcb.a-star.edu.sg

Apoptosis	
Alan PORTER	Cell Death and Human Diseases
Victor YU	Mechanism of Apoptosis in Mammalian Cells
Cell Cycle Control	
Dmitry BULAVIN	Cell Cycle Control and Tumourigenesis
Neal COPELAND/Nancy JENKINS	Mammalian Genetics Laboratory
Yoshiaki ITO	RUNX Genes in Development and Cancer
David LANE	Tumour Suppressor Laboratory
Benjamin LI	DNA Repair and DNA-Methylation in Chemical Carcinogenesis
Yan LUO	Gene Expression and Regulatory Biology
Uttam SURANA	Regulation of the Cell Division Cycle
Cell Structure and Function	
David BALASUNDARAM	Nuclear Transport in *Schizosaccharomyces pombe*
Mingjie CAI	Studies of the Organisation and Function of the Actin Cytoskeleton S. *cerevsiae*
Wanijn HONG	Protein Trafficking in Mammalian Cells
Walter HUNZIKER	Epithelial Cell Polarity
Developmental Biology	
Yun-jin JIANG	Developmental Signaling and Patterning
Vladimir KORZH	Fish Developmental Biology
Baojie LI	Signal Transduction and Developmental Biology
Victor NURCOMBE/Simon COOL	Stem Cells and Bone Tissue Repair
Jinrong PENG	Functional Genomics
Sudipto ROY	Specification of Muscle and Neuronal Cell Fates in Animal Development
Zilong WEN	Molecular and Developmental Immunology
Zhi Cheng XIAO	Axoglial Interaction at Nodes of Ranvier
Xiaohang YANG	Asymmetric Neural Stem Cell Divisions: Genes, Molecules and Mechanism
Genomics	
Sydney BRENNER/Byrappa VENKATESH	Molecular Genetics
Infectious Diseases	
Seng Gee LIM/Yee Joo TAN/Wanjin HONG	Collaborative Anti-Viral Research
Ding Xiang LIU	Molecular Virology and Viral Pathogenesis
Yue WANG	Molecular and Cellular Biology of *Candida albicans*
Lianhui ZHANG	Microbial Quorum Sensing
Signal Transduction	
Xinmin CAO	Regulation and Function of Stat Proteins in Cell Signaling
Graeme GUY	Signal Transduction of Cytokines and Growth Factors
Louis LIM/Thomas LEUNG/Edward MANSER	Neural Differentiation and Degeneration
Vinay TERGAONKAR	NFκB Signaling in Human Ailments
Daoxin XIE	Ubiquitin-Dependent Proteolysis and Jasmonate Signaling
Structural Biology	
Bob ROBINSON	Actin Structure and Cell Movement
Haiwei SONG	Translation Termination and Nonsense-Mediated mRNA Decay
Kunchithapadam SWAMINATHAN	Structure-Function Studies of Proteins by X-Ray Crystallography

TENURE-TRACK FACULTY POSITION
ENDOCRINOLOGY

DEPARTMENT OF BIOLOGICAL SCIENCES
THE UNIVERSITY OF SOUTHERN MISSISSIPPI

The Department of Biological Sciences at The University of Southern Mississippi invites application for a tenure-track assistant professor position in Endocrinology. Research emphases include, but are not limited to, behavioral endocrinology, comparative endocrinology, or molecular endocrinology. The successful candidate will join our rapidly growing department with strong research programs in ecology, molecular, cellular and organismal biology. State-of-the-art facilities are available, including resources associated with the Mississippi Functional Genomics Network, an NIH funded consortium that spans the disciplines of genomics, proteomics, cellomics and bioinformatics (**http://mfgn.usm.edu/mfgn/**). A competitive salary commensurate with qualifications and experience, competitive startup package and new modern lab space will be provided.

The University of Southern Mississippi, a Carnegie Research I institution with over 14,000 students, is located in Hattiesburg, Mississippi, near Gulf Coast resorts and abundant opportunities for outdoor recreation. Hattiesburg is the medical, commercial and cultural center of south Mississippi and is ranked in the top five small metropolitan areas in the United States. The Department of Biological Sciences is comprised of over thirty faculty and offers Bachelor's degrees in Biological Sciences and Marine Biology. Over 70 graduate students currently pursue Master's and doctoral degrees. Further information about the Department of Biological Sciences may be found at **http://www.usm.edu/biology/** .

The successful candidate will be expected to establish an active, extramurally funded research program, mentor graduate students, and participate in undergraduate/graduate teaching in his/her area of expertise. A doctorate in appropriate discipline and postdoctoral research experience are required.

Applicants should submit a letter of application, curriculum vitae, statement of research plans, copies of pertinent reprints and three letters of reference to: **Dr. Shiao Wang, Endocrinology Search Committee, Dept. of Biological Sciences, The University of Southern Mississippi, 118 College Drive #5018, Hattiesburg, MS 39406-0001**. Review of applications will begin **January 20, 2006** and continue until the position is filled.

The University of Southern Mississippi is an Affirmative Action/Equal Opportunity Employer/ Americans with Disabilities Act Institution.

DELAWARE STATE UNIVERSITY
The Department of Biology
Tenure Track Faculty Positions in Neuroscience and Biotechnology

As part of a major University initiative to expand research activities, the **Department of Biology** seeks appointments in **3 faculty positions**. We seek outstanding scientists whose research interests complement existing strengths in the Department and across the University, and who are committed to developing strong programs in research and teaching.

For two of the positions we are seeking candidates with expertise in **cellular and molecular neuroscience** and research involving molecular physiology and molecular genetics. For the third position we are seeking a scientist applying the techniques of molecular genetics, genomics or proteomics to the **study of cancer**, although other areas will be considered. Successful candidates will be expected to develop an externally funded research program and to teach advanced courses related to their expertise.

Interested candidates should submit a curriculum vitae, a graduate transcript, a summary of research plans, a statement of teaching interest/philosophy, and contact information for 3 persons from whom letters of recommendation can be requested to: **Dr. Gustav Ofosu, Chair, Department of Biology, Delaware State University, 1200 North DuPont Hwy, Dover, DE 19901**. Candidates may also apply online through the university website: **www.desu.edu**. Review of applications will begin **January 16, 2006** and will continue until the positions are filled.

DSU is an Equal Opportunity, Affirmative Action Employer. Applications from Minorities and Women are encouraged.

TENURE-TRACK FACULTY POSITION
DEVELOPMENTAL BIOLOGIST

DEPARTMENT OF BIOLOGICAL SCIENCES
UNIVERSITY OF SOUTHERN MISSISSIPPI

The Department of Biological Sciences at The University of Southern Mississippi invites application for a tenure-track assistant professor position in Developmental Biology. The successful candidates will join our rapidly growing department with strong research programs in molecular biology, genomics/bioinformatics, cellular and organismal biology, and ecology. A competitive salary commensurate with qualifications and experience, competitive startup package, new modern lab space, and state-of-the-art facilities will be provided. The successful candidate will have the opportunity to take advantage of resources provided by the Mississippi Functional Genomics Network, a competitively funded NIH consortium that spans the disciplines of genomics, proteomics, cellomics and bioinformatics (**http://mfgn.usm.edu/mfgn/**).

The University of Southern Mississippi, a Carnegie Research I institution with over 14,000 students, is located in Hattiesburg, Mississippi, near Gulf Coast resorts and abundant opportunities for outdoor recreation. Hattiesburg is the medical, commercial and cultural center of south Mississippi and is ranked in the top five small metropolitan areas in the United States. The Department of Biological Sciences is comprised of over thirty faculty and offers Bachelor's degrees in Biological Sciences and Marine Biology. Over 70 graduate students currently pursue Master's and doctoral degrees. Further information about the Department of Biological Sciences may be found at **http://www.usm.edu/biology/** .

The successful candidate will be expected to establish an active, extramurally funded research program, mentor graduate students, and participate in undergraduate/graduate teaching in his/her area of expertise. A doctorate in appropriate discipline and postdoctoral research experience are required.

Applicants should submit a letter of application, curriculum vitae, statement of research plans, copies of pertinent reprints and three letters of reference to: **Dr. Glen Shearer, Developmental Biology Search Committee, Dept. of Biological Sciences, The University of Southern Mississippi, 118 College Drive, # 5018, Hattiesburg, MS 39406-0001.** Review of applications will begin **January 20, 2006**, and continue until the position is filled.

The University of Southern Mississippi is an Affirmative Action/Equal Opportunity Employer/ Americans with Disabilities Act Institution.

McGill
Parasite Immunologist (Assistant/Associate Professor)

The Institute of Parasitology at McGill University (see **http://www.mcgill.ca/parasitology/**) is seeking to appoint a tenure track Assistant/Associate Professor with experience and research interests in the immunology of parasite infections. The appointee will hold a PhD and have a demonstrated track record in immunology and attracting research funding. We seek applicants with research experience in mechanisms of acquired immunity, immunopathogenesis, immunomodulation of host responses and/or vaccine discovery. The appointee is expected to develop a research program supported by external funding and to teach in the undergraduate and graduate programs at McGill. The appointee will become a member of the FQRNT Centre for Host-Parasite Interactions (**http://www.mcgill.ca/chpi/**). McGill has a dynamic research community with a commitment to develop research and teaching in infectious diseases and the application of genomic and proteomic approaches.

Forward a CV, a summary of your proposed research plans and the names of 3 referees by **17 March 2006** to: **Professor Terry Spithill, Director, Institute of Parasitology, McGill University, 21111 Lakeshore Rd, Ste. Anne de Bellevue, Quebec, Canada. H9X 3V9**. For further information, see above web site or call **(514) 398-7954**.

All qualified candidates are encouraged to apply; however, Canadian citizens and permanent residents of Canada will be given priority. McGill University is committed to equity in employment.

UMDNJ - NEW JERSEY MEDICAL SCHOOL

■ SMALL ANIMAL SURGEON

The Department of Cell Biology and Molecular Medicine at the University of Medicine and Dentistry of New Jersey - New Jersey Medical School is seeking an experienced Small Animal Surgeon to join their team of interdisciplinary researchers. A large focus of the department is cardiovascular research. The qualified candidate should be proficient in mouse survival surgery.

Interested applicants should send their CV along with three references to **Stephen F. Vatner, M.D., Chair, Department of Cell Biology and Molecular Medicine, UMDNJ-New Jersey Medical School, 185 South Orange Avenue, MSB G609, POB 1709, Newark, NJ 07101-1709.** UMDNJ is an AA/EO Employer, M/F/D/V.

UMDNJ
NEW JERSEY MEDICAL SCHOOL
University of Medicine & Dentistry of New Jersey

Postdoctoral Positions Anticancer Drug Development

NIH-funded postdoctoral positions are available immediately in the Division of Drug Development of the Nevada Cancer Institute (website: **http://www.nevadacancerinstitute.org**). Candidates must have a Ph.D. or M.D. Ph.D. degree with a research background in molecular pharmacology, clinical and preclinical pharmacology and drug metabolism. Expertise in molecular biology, in vivo and molecular imaging, analytical chemistry and/or transgenic mouse technology is required. We are seeking candidates who are self-motivated and career-oriented to join an exciting highly interactive research team focused on translational research.

Applicants should have a publication record in leading peer-reviewed journals and demonstrated potential to obtain extramural funding. To apply, please submit a curriculum vitae, a brief statement of research interests, copies of 2-4 representative publications, and 3 letters of reference sent to:

Giuseppe Pizzorno, Ph.D., Pharm.D.
Vice President of Research Operations and Head of Drug Development
c/o John Gilani
Nevada Cancer Institute
10000 W. Charleston # 140
Las Vegas, NV 89135
or email to: **jgilani@nvcancer.org**

Review of applications will commence immediately and continue until positions are filled.

DIRECTOR

Christopher S. Bond LIFE SCIENCES CENTER

at the

University of Missouri-Columbia

The University of Missouri-Columbia (MU) invites nominations and applications for Director of the Christopher S. Bond Life Sciences Center.

THE POSITION

We seek a dynamic, internationally recognized scientist to provide leadership to expand and implement the vision of the Center. The Bond Life Sciences Center is a key part of a campus plan to take advantage of the substantial interdisciplinary opportunities provided by the recent and rapid growth in both the numbers of MU's faculty and the size and quality of our resources in the Life Sciences. The Director, reporting to the Vice Provost for Research, will play a pivotal role in the shaping of the campus-wide vision for interdisciplinary life sciences, and in the implementation of that vision, by leveraging a sizeable operating budget with campus departments and the Office of Research.

THE CENTER

The $64 million Christopher S. Bond Life Sciences Center was opened in the fall, 2004, and was designed and equipped explicitly to facilitate interdisciplinary research in the life sciences. The success over the first year has exceeded all expectations. A set of interdisciplinary research themes have been defined, and the themes are the focus of 30 highly productive, entrepreneurial, and collaborative faculty-led research teams. We expect to add 8-10 new teams in the near future. The Bond Center is the hub for interdisciplinary life sciences research and innovation at MU and houses core facilities for DNA analysis, proteomics, and molecular cytology, a state-of-the-art transgenic mouse facility, a BSL-level 3 laboratory, and the campus-wide Offices for Industrial Research and Undergraduate Research. The website, lifesciences.missouri.edu, describes the activities of current faculty, research themes and the Bond Center's physical facilities.

QUALIFICATIONS AND RESPONSIBILITIES

Nominees and applicants must have a Ph.D., M.D. or equivalent degree in an area of the Life Sciences with qualifications for a tenured full professorship in an academic department and a record of outstanding research accomplishments. The position demands a commitment to interdisciplinary Life Sciences; exceptional interpersonal and communication skills; a willingness to interact with public and private groups in the role of a leader of MU's and the State of Missouri's life science efforts; administrative, intellectual and programmatic research leadership, as well as leadership in pre-doctoral and post-doctoral training; and an appreciation of the land-grant mission.

THE LOCATION

The University of Missouri-Columbia is a comprehensive AAU, Carnegie Doctoral Research-Extensive, land-grant institution with more than 2,000 faculty — approximately 700 in the life sciences — more than 20,000 undergraduates and over 6,000 graduate and professional students. MU's research expenditures last year were approximately $230 million and growth in federal research dollars over the last ten years has been one of the fastest of any AAU public institution. MU's interdisciplinary environment is fueled by being one of six American universities that includes medicine, veterinary medicine, engineering, agriculture and law on a single campus. In addition, the campus houses the nation's leading School of Journalism, as well as the world's most powerful university-based research reactor, which plays a major role in MU's biological imaging and radiopharmaceutical research. Columbia, Missouri is consistently ranked as one of the top 20 places to live in the U.S.

THE APPLICATION

Nomination letters, or letters of application including a curriculum vitae and the names and contact information of five references, should be submitted electronically to carterka@ missouri.edu or via the website http://lifesciences.missouri.edu/director or by mail to Karla Carter, room 105 Christopher S. Bond Life Sciences Center, 1201 Rollins Street, University of Missouri-Columbia, Columbia, MO 65211. Review of applications will begin February 1, 2006 and continue until the position is filled. Questions can be directed to the Chair of the Search Committee, Dr. Judy Wall (wallj@missouri.edu; 573-882-8726), or Vice Provost for Research, Dr. Jim Coleman (colemanjs@missouri.edu; 573-882-9500).

The University of Missouri is an AA/EOE. To request ADA accommodations, contact (573) 884-7278 (V/TTY). Women and Minorities are encouraged to apply.

MICHIGAN STATE UNIVERSITY

CWS Post-doctoral Fellowship Program

The Michigan State University Center for Water Sciences (CWS) invites applications for five post-doctoral fellowships working in water-related sciences. The CWS is dedicated to promoting the integration of traditional fields of science to address water-related issues which focus on ecosystems and human health. We are particularly interested in candidates working in one or more of our priority research areas: antibiotics and microbial resistance, waterborne disease agents, microbial biodiversity, biogeochemical and hydrologic processes, watershed influences on aquatic ecosystems, effects of stressors with global origins, ecosystem services and human activities in watersheds, algal toxins and water supply, perfluorinated organic compounds, and international programs investigating effects of climate, landscape, and cultural diversity on the coupling of human and ecological systems.

Fellows will be supported for two years with a salary of $40,000 per year plus benefits.

Post-doctoral Fellows will be matched with CWS host faculty working on projects related to priority research areas. Applications will be accepted until positions are filled; review of applications begin January 2006. Applicants should have a PhD in a relevant field. Applicants who are not US citizens or permanent residents must provide documentation for employment authorization in the US. Interested individuals should prepare (1) a letter of application, (2) curriculum vitae, (3) names and contact information of three references, and (4) a statement describing your research interests and goals, professional experience, and how they relate to the mission and priority research area(s) of CWS. Send application materials to: Dr. Erin Dreelin, Center for Water Sciences, 13 Natural Resources, Michigan State University, East Lansing, MI 48824, dreein@msu.edu. For more information about the CWS research programs, contact Co-Directors Joan Rose (rosejo@msu.edu) and R. Jan Stevenson (rjstev@msu.edu) and see www.espp.msu.edu/cws.

CWS Center for Water Sciences

MSU IS AN AFFIRMATIVE ACTION, EQUAL OPPORTUNITY INSTITUTION.

SK BIO-PHARMACEUTICALS

- **BIOCHEMIST**
  Metabolites identification (PhD)
- **ELECTROPHYSIOLOGIST**
  Ion channel/patch clamping (PhD)
- **TOXICOLOGIST/PATHOLOGIST**
  Preclinical toxicity (DVM)
- **CLINICAL/MEDICAL DIRECTOR**
  Experience in CNS (MD/PhD)
- **ANALYTICAL CHEMIST**
  Drug (pre)formulation (PhD)
- **BUSINESS ADMINISTRATOR**
  Pharmaceutical business (MBA)
- **REGULATORY AFFAIRS LEADER**
  Industry regulatory experience

Candidates with pharmaceutical industry experience desired. Qualifying candidates should forward resume/CV with cover letter to:

Human Resources Department
SK Bio-Pharmaceuticals
140A New Dutch Lane
Fairfield, NJ 07004

Fax: (973) 227-4488
Email: cson@skbp.com
www.skbp.com

Virginia Tech
VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY

Cluster Hires
College of Science

The College of Science at Virginia Tech is now in its third year of cluster hiring to enhance and strengthen research in strategic areas. Four broad areas remain the foci: **nanoscale science, computational science, infectious diseases** and **developmental science** across the life span.

Cluster hiring is coordinated with similar activities with the College of Agriculture and Life Sciences and the College of Liberal Arts and Human Sciences. Twenty-one faculty members were appointed in the college under the cluster approach in the first two years and similar results are expected this year.

Appointments are possible within the disciplines of biology, chemistry, economics, geosciences, mathematics, physics, psychology, and statistics. See specific position descriptions and instructions at **www.cos.vt.edu/jobs**.

Both junior- and senior-level candidates are encouraged to apply, as well as experimental and theoretical scientists.

Virginia Tech is an AA/EEO employer and an NSF Advanced institution; applications from members of underrepresented groups are especially encouraged.

IANR

University Of Nebraska Lincoln

DIRECTOR
SCHOOL OF NATURAL RESOURCES
THE UNIVERSITY OF NEBRASKA-LINCOLN

The University of Nebraska-Lincoln invites applications for the Director of the School of Natural Resources. This position is an excellent opportunity for a recognized scientist with proven academic and administrative skills to lead a multi-disciplinary faculty and support staff. The University is looking for a candidate with a strong record of achievement and a commitment to an interdisciplinary approach to address existing and emerging natural resource, ecological, and environmental issues. Candidates should be knowledgeable of and committed to the teaching, research, extension education and public service missions of a land grant institution. A complete position announcement is found at **http://snr.unl.edu**. Candidates can also review the mission and programs of the School at this web site.

To apply for this position, access the web site **http://employment.unl.edu**. Search for requisition number **051022**, Director of the School of Natural Resources. Complete the faculty academic administrative information form, attach a letter of application, curriculum vitae, and list of references. Review of applications will begin **February 1, 2006**, and will continue until the position is filled.

The University of Nebraska-Lincoln is committed to a pluralistic campus community through Affirmative Action and Equal Opportunity and is responsive to the needs of dual career couples. We assure accommodation under the Americans with Disabilities Act; contact Linda Arnold at 402-472-3802 for assistance.

Galveston

MARINE INVERTEBRATE ZOOLOGY
Texas A&M University at Galveston (TAMUG)

The Marine Biology Department (MARB) seeks to fill a 9-month tenure-track assistant professor position in Marine Invertebrate Zoology for the fall of 2006. The successful candidate is expected to teach an undergraduate comprehensive invertebrate zoology course and develop graduate level courses in his/her specialty, advise graduate students, and develop an externally funded research program. Applicants must have a PhD, with post-doctoral experience. Areas of specialization include, but are not restricted to, developmental biology, ecology, evolution, molecular systematics, parasitology, physiology and taxonomy. A commitment to teaching excellence is required and prior teaching experience is desirable. Competitive start-up funds are available.

With approximately 1700 undergraduates and 50 graduate students, all enrolled in marine or maritime degree programs, TAMUG is the coastal branch campus of Texas A&M University (TAMU). The main campus has a current enrollment of approx. 44,000 students, and TAMU is the Land, Sea and Space Grant University of Texas. Graduate degrees pursued by TAMUG students at College Station include Biology, Oceanography, Ocean Engineering, Rangeland Ecology and Management, and Wildlife and Fisheries Sciences. MARB is the largest department at TAMUG, with approximately 550 undergraduates and 30 graduate students. TAMUG, as TAMU's 'window to the sea,' houses the Texas Maritime Academy, which operates the T/S TEXAS CLIPPER. TAMUG is headquarters for the Texas Institute of Oceanography (TIO), Laboratory for Environmental Research (LOER), and the Institute of Marine Life Sciences (IMLS). Additional information about TAMUG and MARB can be found at **http://www.tamug.edu**.

Review of applications will begin **January 31, 2006**, and will continue until the position is filled. Please submit curriculum vitae, statements of teaching and research interests, and full contact information for four references to **Dr. Jaime R. Alvarado Bremer**, in PDF format via e-mail (**alvaradj@tamug.edu**), or by mail to: **Marine Invertebrate Zoologist Search Chair, Marine Biology Department, Texas A&M University at Galveston, Galveston, Texas 77553-1675, USA**.

Texas A&M University is an Equal Opportunity/Affirmative Action Employer that accommodates individuals with disabilities. Individuals requesting a disability accommodation should contact the Human Resources Department. Proper documentation of identity, official transcripts and valid employment authorization required at the time of employment.

SCIENCE AND TECHNOLOGY CENTER IN UKRAINE
U.S. DEPUTY EXECUTIVE DIRECTOR

The Office of Cooperative Threat Reduction in the Bureau of International Security and Nonproliferation, Department of State, seeks candidates for the U.S. Deputy Executive Director for the Science and Technology Center of Ukraine (STCU).

The STCU serves as a critical multilateral effort to redirect former Weapons of Mass Destruction (WMD) scientists in Ukraine, Azerbaijan, Georgia, Moldova, and Uzbekistan and foster sustainable scientific research at institutes in the member states. The position, located in Kyiv, Ukraine, is one of the top management positions at the Center. The incumbent reports to the STCU's Executive Director. The incumbent takes the lead in the Center's sustainability promotion activities, an area of extreme importance to the United States, manages the STCU's growing governmental and non-governmental partnership program, and oversees the Center's patent processes. S/he serves as the primary liaison between the multilateral STCU and the U.S. Party, and communicates regularly with representatives of the other Parties, Canada, the EU, and Ukraine.

The Deputy Executive Directors (one each from Canada, the EU, Ukraine, and the U.S.) serve as the STCU's leaders, taking the initiative to address problems, resolve issues, interact with governmental, diplomatic, and scientific officials, assist in strategic planning, assist in overall policy development and implementation, and promote the most effective and efficient execution of STCU programs and activities.

The ideal candidate for this position is a natural leader with a scientific background who is thoroughly familiar with large-scale science and technology management, is comfortable in a multilateral setting, and can assume a leadership role immediately upon arrival in Kyiv. Excellent communication and organizational skills, an understanding of U.S. governmental processes, and diplomatic abilities are a must.

As the current U.S. Deputy Executive Director has completed his tour of duty, the U.S. must identify a candidate as soon as possible to forward the name to the STCU Executive Board for immediate consideration. The candidate selected must be willing and able to relocate to Kyiv immediately after selection.

The U.S. Deputy Executive Director, like the other STCU Deputy Executive Directors, is appointed for a term of two years. The term may be extended. The Deputy Executive Director serves at the pleasure of the Governing Board. The incumbent travels on a U.S. diplomatic passport and moving expenses are covered.

Further information on the STCU is available on its website, **www.stcu.int**.

Please send your resume to:

Phil Dolliff, Acting Deputy Director
ISN/CTR
Room 3327, Department of State
Washington, DC 20520

no later than **December 30, 2005**

Desirable Qualifications, Skills, and Attributes:

Technical background: Ph.D. or equivalent experience in a scientific field, experience in leading or having a major leadership role in large research initiatives, particularly international, multiparty/multi-institute initiatives.

Managerial expertise: Program or project management experience, particularly involving teams and people from a variety of national and cultural backgrounds; management experience in program creation and development, budget planning, and program execution; successful experience in a results-oriented, management-by-objective work environment.

Technology Transfer Experience: Knowledge of technology transfer issues, including general knowledge of patent application processes, appropriate handling of proprietary knowledge, and the beneficial exploitation of research.

Public Experience: Experience in working in both the academic and public sector/government environments; experience in science and technology interaction and communications at an international level.

Language Requirement: Fluency in English is required; knowledge of Russian or Ukrainian language is a consideration but not a requirement.

Citizenship: The incumbent must be a U.S. citizen.

Princeton Seeks Leader to Spearhead Engineering and Life Sciences Initiative

Princeton University seeks applications for a tenured faculty opening that we view as a "transformative hire" to lead a major initiative in engineering and the life sciences. The ideal candidate will be an established research leader who has an outstanding scholarly record comprising interdisciplinary efforts that link engineering, biology, and related areas.

More than half the faculty in Princeton's engineering school, including some of its most renowned researchers, work at the intersection of engineering and the life sciences. Existing strengths include biomolecular engineering, bioinformatics, robotic biomimicry, biomaterials, and ecosystem biocomplexity. In addition, leading faculty in Princeton's life sciences departments have active collaborations with engineering faculty. Building on and expanding ongoing research activities in engineering and the life sciences is a central thrust of Princeton's strategic vision, and we plan to establish new focus areas for significant growth. The successful candidate will play a major role in defining this initiative, setting its research agenda and outlining its required resources. The overall goal is to leverage considerable university resources into the development of a truly world-leading research thrust for engineering and the life sciences. The effort will involve new faculty appointments and state-of-the-art research spaces. In addition to individual achievements, the successful candidate will possess outstanding leadership skills and a sharp vision for establishing a major university effort in this area.

About Princeton University: As a research university, Princeton seeks to achieve the highest levels of distinction in the discovery and transmission of knowledge and understanding, and in the education of undergraduate and graduate students. More than 700 faculty members, who are leaders in their respective disciplines, instruct Princeton's 4,600 undergraduate students and 2,000 graduate students. The town of Princeton, NJ includes a population of roughly 30,000 people with outstanding schools and excellent neighborhoods. The central New Jersey area is well-suited for dual-career couples, with numerous large companies nearby, and within commuting distance of New York and Philadelphia.

Candidates should submit a curriculum vitae and a statement of research and teaching interests to **cels-fac-search@princeton.edu** or to: **Engineering and Life Sciences search committee, c/o Dr. Victoria Dorman, School of Engineering and Applied Science, Engineering Quadrangle, Princeton University, Princeton, NJ 08544**. Questions can be directed to **cels-fac-search@princeton.edu**. The committee will begin reviewing applications on **January 1, 2006**. For information about applying to Princeton and how to self identify, please link to **http://web.princeton.edu/sites/dof/ApplicantsInfo.htm**.

UCSF

Faculty Position in Physiology

The Department of Physiology and the Program in Biological Sciences at the University of California San Francisco (UCSF) seek an assistant professor (tenure track) taking cellular, molecular, genetic or other novel experimental approaches to problems in physiology. The successful applicant will occupy laboratory space at the new Mission Bay campus of UCSF and will be expected to establish an exciting research program and participate in graduate and postdoctoral training.

Complete applications should be received by **January 16, 2006**, to ensure full consideration. Please send a curriculum vitae, reprints of one or two key publications, a two-page summary of past research and future goals, electronically (PDF format) to: **2006_phy_Ingraham@physio.ucsf.edu**. Have three letters of recommendation sent to:

Physiology Search Committee
c/o Janet Williams
Department of Physiology
1550 4th Street, Rock Hall, Room 183
University of California
San Francisco, CA 94143-2610

UCSF is an Affirmative Action/Equal Opportunity Employer. The University undertakes affirmative action to assure equal employment opportunity for underutilized minorities and women, for persons with disabilities, and for Vietnam-era veterans and special disabled veterans.

WAYNE STATE UNIVERSITY

Biology Faculty Positions

The Department of Biological Sciences at Wayne State University has three tenure-track openings for new faculty. Rank will be dependent upon qualifications. Preference will be given to candidates who utilize state-of-the-art approaches to study complex biological problems with the potential to integrate their research programs with existing multidisciplinary research groups.

Ecology/organismal biology: Areas of interest include, but are not limited to, aquatic ecology, behavioral ecology, evolutionary ecology, microbial ecology, phylobiogeography, organismal biology and population ecology. **Position Number 032356**.

Microbiology: Areas of interest include, but are not limited to, molecular microbiology, medical microbiology, microbial genomics, bioinformatics, microbial physiology/biochemistry, virology, biodefense, emerging diseases, drug development and antibiotic resistance. **Position Number 032324**.

Biochemistry: Areas of interest include, but are not limited to, structure-function relationships, protein and/or nucleic acid biochemistry, molecular basis of metabolic diseases and design/synthesis of therapeutics. **Position Number 032323**.

The Department is primarily housed in the six-story Biological Sciences Building that contains modern, spacious research laboratories and outstanding facilities for microscopic imaging, cell culture and nucleic acid analyses. Vertebrate and invertebrate animal facilities are also available. Wayne State University is a large, comprehensive, nationally ranked research institution that offers generous start-up packages. Applicants must have a Ph.D. degree, postdoctoral experience and an outstanding record of research achievement. Successful applicants are expected to establish and maintain vigorous, externally funded research programs and participate in graduate and undergraduate education. Applications will be considered only if they are received on-line at **jobs.wayne.edu**. Applicants must indicate the position(s) for which they are applying by marking the corresponding Position Number(s). In addition to their online application that includes curriculum vitae and cover letter, applicants must submit a statement of research plans, a statement of teaching interests and philosophy and have three letters of reference sent to: **Chair, Faculty Search Committee, Department of Biological Sciences, Wayne State University, 5047 Gullen Mall, Detroit, MI 48202**. Review of applications will begin immediately and the search will remain open until the positions have been filled. Applications will be considered only when all materials have been received.

Wayne State University is an Affirmative Action/Equal Opportunity Employer. Women and members of minority groups are especially encouraged to apply.

FELLOWSHIPS

Charles H. Best Postdoctoral Fellowship

BANTING AND BEST DEPARTMENT OF MEDICAL RESEARCH University of Toronto

Charles H. Best Postdoctoral Fellowships are awarded each year to highly qualified graduates (2 years or less postgraduate) in the field of molecular, genetic and genomic research. The two year fellowship is tenable in the Banting and Best Department of Medical Research at the University of Toronto. Individual research programs include studies on functional genomics, gene expression, signal transduction, development, membrane transport and protein structure.

Applications should be addressed to: **Dr. Henry Krause, Chair, C.H. Best Fellowship Committee, Room 502, 160 College Street, Toronto, Ontario, Canada, M5S 3E1**, and should include a curriculum vitae, transcripts and three letters of reference. Applicants are also strongly encouraged to contact one or two potential supervisors whose interests and e-mail addresses are posted on our Departmental WEB page (**http://www.utoronto.ca/bandb**). The deadline for applications is **January 15, 2006**.

Chief, Biochemical Science Division
National Institute of Standards and Technology

Applications are invited for candidates to lead the Biochemical Science Division, at NIST in Gaithersburg, Maryland. The Division serves as the Nation's reference laboratory for providing the measurements, standards, and data needed to enhance U.S. industry's productivity and competitiveness, assure equity in trade, foster innovation, improve public health, and provide quality assurance for measurements used in advancing the commercialization of biochemical sciences. The Division, through its programs, supports NIST's mission to develop and promote measurement, standards, and technology to enhance productivity, facilitate trade, and improve the quality of life. The Division's research is carried out in four groups: (1) DNA Measurements, (2) Biospectroscopy, (3) Structural Biology, and (4) Cell and Tissue Measurements. Please refer to the Biochemical Science Division website at **http://www.cstl.nist.gov/biotech/index.html** for more information.

The Chief provides strategic vision and program direction for approximately 50 staff members including approximately 40 Ph.D. scientists with backgrounds in the physical and biological sciences. The Biochemical Science Division is the focus of the NIST effort to address critical measurement and data needs for the rapidly developing biotechnology industry. The Division has established a variety of long-range research programs to maintain critical expertise needed for the development of advanced measurement methods, Standard Reference Materials and databases for use by industry and other research enterprises. The NIST biochemical science program fosters valuable partnerships with industry, universities and other government agencies.

At NIST, Division Chiefs manage resources, devise new programs, and develop program implementation strategies. Applicants must have demonstrated experience in leading and managing research, and a record of sustained scholarly accomplishments. Ideal candidates will have training and experience in the physical, chemical and/or biological sciences. A Ph.D. in physical, chemical or biological sciences is desirable.

The base salary ranges from $103,947 to $140,300, depending on qualifications. U.S. citizenship is required. Applicants should send a resume and three references (names and contact information only) by post or e-mail to: **Mr. Neil Alderoty, Senior Management Advisor, Chemical Science and Technology Laboratory, NIST, 100 Bureau Drive, MS 8300, Gaithersburg, MD 20899; neil.alderoty@nist.gov**. To be considered, complete applications must be postmarked by **January 16, 2006** and received no later than **January 23, 2006**.

At **www.usajobs.opm.gov** see **NIST-2005-ASF** for Biologist, Chemist, or Physicist.

Department of Commerce is an Equal Opportunity Employer.

■ INSTITUTE FOR MOLECULAR BIOSCIENCE (IMB), THE UNIVERSITY OF QUEENSLAND, AUSTRALIA

Biodiscovery Bioassay Officer

The role: Work with biology based research groups at the IMB; identify and assist in prioritising bioassay initiatives; refine and define protocols that address issues of throughput, cost, reliability and relevance; facilitate the bringing online of novel bioassays; liaise with industry representatives to inform IMB researchers of latest technologies; participate in the implementation of innovative biodiscovery programs.

The person: PhD in biochemistry, pharmacology, molecular biology, or an equivalent combination of relevant experience and/or education/training; experience with cell culture, and the operation and application of Elisa, Flow Cytometry, fluorescence and radio-ligand technologies.

Remuneration: AUD$73,432 – $87,201 p.a., which includes employer superannuation contributions of 17%. Full-time, fixed-term appointment at Academic Level B for one year, with renewal subject to funding. The appointment will be at a level commensurate with the successful candidate's experience.

Contact: Obtain the position description and selection criteria online or telephone +61-7-3346-2121 or email b.clyde@imb.uq.edu.au. Contact Prof Rob Capon, telephone +61-7-3346-2979 or email r.capon@imb.uq.edu.au, to discuss the role.

Applications close: 4 January 2006.

Reference No: 3012826.

How to apply:

■ visit **www.jobsatUQ.net** to obtain position description and selection criteria.

CRICOS Provider Number 00025B

San José State UNIVERSITY

Dean of the College of Science

San José State University, located in the heart of Silicon Valley, is seeking a Dean for the College of Science. Under direction of the Provost, the Dean provides the College of Science with strong, experienced collegial leadership in directing the activities of the college.

Academic disciplines include:
- Biological Sciences
- Chemistry
- Computer Science
- Geology
- Mathematics
- Meteorology
- Physics

The ideal candidate will embrace the University's shared values; articulate a vision for the college and foster that vision through implementation; and the promotion of a culture of innovative teaching and scholarly activities.

Visit SJSU's website at
www.sjsu.edu/hr/jobopps/ for details.
EO/AA Employer

EAST STROUDSBURG UNIVERSITY OF PENNSYLVANIA

DEPARTMENT OF BIOLOGICAL SCIENCES
MARINE BIOLOGY - TENURE TRACK FACULTY

East Stroudsburg University invites applications for a full-time, tenure track position beginning Fall 2006. Positions typically fill at the Assistant Professor rank. A Ph.D. in the biological sciences or a related field is preferred; ABDs are considered. Required are (1) a demonstrated commitment to undergraduate teaching and research and (2) a strong background in marine biology (with an area of specialization that should complement departmental interests). Experience in working with diverse populations is preferred. To learn more about diversity at ESU and in our community, visit www3.esu.edu/diversity/home.asp. Teaching responsibilities may include ichthyology, oceanography, marine biology, and marine ecology, as well as introductory biology courses and courses in the successful candidate's area of specialization. The selected individual will be expected to assume administrative responsibilities in support of the Marine Science Program and to teach summer courses at the Wallops Island Marine Science Consortium in Virginia. Service and scholarship are expected.

Full consideration will be given to applications received by January 6, 2006. Send letter of application that indicates area of expertise and experience, curriculum vitae, evidence of quality teaching and an ability to supervise undergraduate research, photocopies of graduate transcripts and three recent letters of recommendation to the attention of: Department of Biological Sciences, Position #O4210, C/O Delores Hart, Faculty Search Coordinator, East Stroudsburg University, East Stroudsburg, PA 18301. Electronic submissions will not be accepted. Official transcripts are required prior to appointment. Final determination will be based upon a successful interview, which may include a teaching demonstration.

Located in the scenic Pocono Mountains within a 90-minute drive of New York City and two hours from Philadelphia, East Stroudsburg University is one of fourteen universities in the Pennsylvania State System of Higher Education. Founded in 1893, with a current enrollment of 6,800, the university continues to build on its sense of history with unique new undergraduate and graduate degree programs and plans for a major new Science and Technology Center. Offering 60 undergraduate degree programs and graduate degrees in 19 areas, the university is experiencing increasing enrollments and is poised for continued growth. Adjacent to the unspoiled Delaware Water Gap National Recreation Area, the surrounding community offers options for suburban, small city, or country living.

PREPARE TO SERVE
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EAST STROUDSBURG UNIVERSITY
FOUNDED 1893

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Minorities and women are strongly encouraged to apply.

Visit our homepage at www.esu.edu

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Postdoctoral Fellowship
Integrative Medicine Program

Background: The popularity of complementary and integrative therapies has grown in recent years, but much research remains to be done before these therapeutic entities can be appropriately evaluated in clinical trials.

Description and objectives: The Integrative Medicine Program at The University of Texas M. D. Anderson Cancer Center is seeking a qualified postdoctoral fellow. The fellow will work with promising natural products or nutraceuticals that are believed to offer distinct advantages in support of the prevention of cancer and to support the health and well being of patients with cancer. Relevant research will include but not necessarily be limited to: (1) pursuit of mechanisms of action; (2) development of appropriate analytical (e.g. HPLC or mass spectrometry) assays to define the product and its metabolism; (3) evaluation of *in vitro* and *in vivo* pharmacology and toxicology; as well as (4) development of appropriate formulations for possible clinical trials. A special interest of the current sponsored research program includes investigation of herb or other natural products that might be considered as either adjunct therapy or even as components of functional foods/drinks for the prevention of cancer.

The University of Texas M. D. Anderson Cancer Center has ranked among the top two cancer centers in the United States for the past 16 years by the US News & World Report, and is located within the Texas Medical Center. Houston is a dynamic, multicultural city with a very affordable cost of living.

Applicants must have earned doctorates in a pertinent discipline (e.g. nutrition, pharmacology, toxicology) or have a medical degree with appropriate training in the basic sciences. Prior experience with natural product research is a distinct advantage. Written and spoken English skills are required. Potential applicants must submit a non-binding letter of intent stating their specific interest in this fellowship opportunity, their Curriculum Vitae (CV), and names and addresses of three or more references. Finalists for the position will be chosen by a committee and interviews and travel to Houston may be required as a part of the application process. The final decision will be made by the Director of the Integrative Medicine Program. Appointments will be for 1 year and renewable for a second year based on performance and funding.

Deadlines: The deadline for applications is **February 15, 2006**.

Inquiries and applications to: **Lorenzo Cohen, PhD, Associate Professor, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Unit 145, Houston, Texas 77030; lcohen@mdanderson.org; www.mdanderson.org.**

Fellowship support provided by The Beverage Institute for Health and Wellness, a subsidiary of The Coca-Cola Company.

www.jcu.edu.au

Lecturer/Senior Lecturer - Physiology (2 Positions)

School of Veterinary & Biomedical Sciences

Townsville/Cairns, Queensland, Australia

The University is seeking to appoint two (2) individuals to contribute to the development of the discipline of Physiology within the School of Veterinary and Biomedical Sciences. The appointees will be expected to contribute to teaching within Veterinary and Biomedical Sciences, Veterinary Science, Medicine, Tropical Agriculture, Medical Laboratory Science, Pharmacy, Occupational Therapy, Physiotherapy and Science programs and to pursue an active research program. Applicants must have a PhD with teaching experience in a tertiary institution, evidence of research output and a demonstrated commitment to quality teaching and research. The provision of a teaching portfolio would be an advantage.

Enquiries to: Professor Phil Summers, telephone +61-7-4781 4758, email Phillip.Summers@jcu.edu.au

Employment Type: Appointment will be full-time on an ongoing basis, subject to a probationary period.

Salary: Lecturer - Academic Level B - A$58,942 - A$69,743 per annum or Senior Lecturer - Academic Level C - A$71,902 - A$82,703. Level of appointment and commencing salary will be determined according to qualifications and experience. Benefits include generous employer superannuation contribution and attractive options for salary packaging.

Applicants must follow the Method of Application procedures (including systematically addressing the Selection Criteria). Further information is available at http://jobs.jcu.edu.au/ or by contacting the Recruitment Officer, Faculty of Medicine, Health and Molecular Sciences, telephone: +61-7-4781 6209; e-mail Adele.Goalder@jcu.edu.au

Applications close on 23rd December 2005. Please quote reference number 5198.

The University reserves the right to invite applications or not to make an appointment.

Equal Opportunity in Employment is University Policy

TMP D58887

>>Always thinking ahead>>

JAMES COOK UNIVERSITY

JCU

Faculty Position in
Molecular Mechanisms of Human Disease
Assistant, Associate, or Full Professor
Brown Medical School
Department of Pathology and Laboratory Medicine

The Department of Pathology and Laboratory Medicine invites applications for a tenure-track position in Molecular Mechanisms of Human Disease with an anticipated start date of July 1, 2006. The appointment will be made at the level of Assistant, Associate or Full Professor depending on the qualifications of the candidate selected. Research space will be provided in a newly renovated laboratory with modern core facilities for genomics and proteomics, transgenic mice, molecular pathology, cell imaging, flow cytometry, NMR, and x-ray crystallography.

Applicants must have a Ph.D., M.D.-Ph.D., or M.D. degree and a demonstrated record of excellence in research. The candidate is expected to develop and maintain a productive, externally funded research program related to molecular mechanisms of human disease. Senior candidates are expected to have peer-reviewed, external funding and a track record of excellence in teaching and training. Candidates appointed at senior ranks must have a national reputation (Associate Professor) or international reputation (Professor) in their field. Preference will be given to applicants with research interests in the area of **genetic susceptibility to cancer or environmental disease, DNA damage and repair, or molecular toxicology/carcinogenesis**. Successful candidates must be committed to excellence in teaching and will have the opportunity to serve as predoctoral and postdoctoral research mentors for the Environmental Pathology Training Program funded by the National Institute of Environmental Health Sciences. Translational research collaborations are facilitated by a Human Tumor Bank and Molecular Pathology Core Laboratory at the nearby Lifespan COBRE Center for Cancer Research Development.

Applications for Associate or Full Professor will be treated with confidentiality and need not include letters of recommendation; a list of references may be requested later. Applications at the Assistant Professor level should include at least three reference letters. Review of all applications, which should include a curriculum vitae, a description of career objectives, and future research plans, will commence on **January 15, 2006**, and will continue until the position is filled. Contact address: **Agnes B. Kane, M.D., Ph.D., Professor and Chair, Department of Pathology and Laboratory Medicine, Brown University, Box G-E534, Providence, RI 02912**.

Brown University is an EEO/AA Employer and invites applications from women, minorities and protected persons.

US Environmental Protection Agency (EPA)
Office of Research and Development (ORD)

EPA's Office of Research and Development (ORD), Office of the Science Advisor (OSA) is seeking a candidate for a Scientific/Technical (ST) Professional position as Human Subjects Research Review Official. Highly qualified scientific leaders currently engaged in matters related to human research ethics and subject safety are sought to lead this high level position.

This position is responsible for providing high-level scientific leadership and overall coordination relating to human research ethics and subject safety. Other responsibilities include representing ORD on Agency Human Subjects Workgroups as well as other Federal Oversight Offices such as the Office of Human Research Protection. The incumbent will also provide advice and recommendations which may serve as a basis for policy decisions in areas related to human subjects' research. The incumbent will also be responsible for the Human Subjects Research Review Protocol, serve as the key liaison for EPA in interactions with Institutional Review Boards; develop, evaluate and oversee training and staff education related to the ethical and safe conduct of human studies; and provide guidance to human research investigators in preparing protocols, consent forms, questionnaires, etc. Appointment is subject to the successful completion of a background security investigation. This position is subject to random drug testing.

The minimum rate of basic pay for a Scientific/Technical (ST) position equals 120 percent of a GS-15 step 1 rate of basic pay (e.g., $120,155 per annum). This position will be based in Washington, D.C.

Applicants should submit a CV and a vision statement to: **Jayne Ramsey at US EPA/ORD (8101R), 1200 Pennsylvania Avenue, N.W., Washington, D.C. 20460**. For more information, please go to **http://www.epa.gov/ORD/htm/jobs_ord.htm**, or you may contact **Jayne Ramsey** at **(202) 564-6736** or **ramsey.jayne@epa.gov.** Applications must be postmarked by **December 23, 2005**.

U.S. Citizenship Required
EPA is an Equal Opportunity Employer

Pediatric Hematology-Oncologist

The Section of Pediatric Hematology/Oncology at **Scott and White Clinic** and the **Texas A&M University System Health Science Center College of Medicine** (TAMUS HSC-COM) are seeking a clinician scientist with current research grants for a faculty position in a rapidly growing program. The candidate should be BE/BC in pediatric oncology and committed to an academic career. The successful candidates will join and enhance ongoing efforts in basic and translational research, with an institutional commitment to building a world-class experimental therapeutics program. An outstanding start-up package includes high quality laboratory space, excellent benefits and competitive salaries commensurate with academic qualifications. The position guarantees 75% protected time for research activities.

Scott & White Clinic is a 500+ physician directed multi-specialty group practice that is the leading provider of cancer care in Central Texas. Scott and White Clinic and the 486 bed tertiary Scott & White Memorial Hospital is the main clinical teaching facility for TAMUS HSC-COM. Outstanding clinical practice and laboratory facilities on campus that perform state of the art molecular and cellular biology research, flow cytometry, genomics and biostatistics are in place to support the research effort.

Please contact: **Don Wilson, M.D. Professor and Chairman, Department of Pediatrics, Scott & White, 2401 S. 31st, Temple, TX 76508. (800)725-3627 dwilson@swmail.sw.org Fax (254) 724-4974.**

For more information about Scott & White, please visit www.sw.org For Texas A&M www.tamhsc.edu. Scott & White is an equal opportunity employer.

MAYO CLINIC

Statistical Genetics, Genomics of Addiction

Rochester, Minnesota

Mayo Clinic in Rochester, Minnesota is seeking a full-time faculty member with expertise in statistical genetics. This newly funded program – The S.C. Johnson Genomics of Addiction Program – focuses on the analysis of complex genomic data relevant to the understanding of the biological basis of addiction to alcohol and other substances of abuse. The successful candidate will be an outstanding investigator with research accomplishments and scholarship in the application of statistical genetics to the study of complex genetic diseases and traits. This is a joint appointment in the Department of Psychiatry and Psychology and the Division of Biostatistics. The appointed faculty will join a multidisciplinary community of scientists and clinician-investigators studying the genetic basis of addictions with cutting edge research programs, and an expanding staff in statistical genetics and bioinformatics.

Minimum qualifications include a Ph.D. degree in statistics, biostatistics, bioinformatics, or a closely aligned quantitative area, with computational experience, as well as excellent oral and written communication skills. A competitive compensation and benefits package is provided.

To learn more about Mayo Clinic and Rochester, MN, please visit **www.mayoclinic.org**.

Applicants should submit their curriculum vitae with a cover letter summarizing their qualifications and research goals, as well as three letters of recommendation, sent separately. Material should be submitted by February 1, 2006, to:

Daniel J. Schaid, Ph.D.
Harwick 7
Mayo Clinic
200 First Street, S.W., Rochester, MN 55905
Email: **schaid@mayo.edu**; Phone: (507) 284-0639

Mayo Foundation is an affirmative action and equal opportunity educator and employer. Post offer/pre-employment drug screening is required.

Faculty Position
The University of California at San Diego
Section of Cell and Developmental Biology
Division of Biological Sciences
http://biology.ucsd.edu/

The Section of Cell and Developmental Biology in the Division of Biological Sciences at UCSD invites applications for a new faculty position. The appointment will be at the Assistant Professor level. Candidates pursuing innovative research in all areas of modern cell biology are encouraged to apply. Research areas include, but are not restricted to: intracellular compartmentation, membrane/cytoskeleton dynamics and locomotion, cell cycle, growth regulation, signal transduction, and morphogenesis. The successful candidate is expected to have a broad interest in cell biology and complement existing strengths in the Section of Cell and Developmental Biology and within the Division of Biological Sciences. The primary criteria for selection will be research excellence and potential. All candidates must have a Ph.D., M.D., or an equivalent degree. The successful candidate is expected to participate in the undergraduate and graduate teaching curriculum. The level of appointment will be commensurate with qualifications and experience. Salary based upon University of California pay scale.

Complete applications received by **January 20, 2006** will be assured of consideration. Applicants should submit a curriculum vitae, a complete list of publications, a short statement of research interests and scientific goals, and three letters of recommendation (forwarded separately) to:

Cell Biology Search Committee
Section of Cell and Developmental Biology
Division of Biological Sciences
Attn: Jennifer Roth - Mail Code 0380-B
Natural Sciences Building
University of California, San Diego
9500 Gilman Drive
La Jolla, CA 92093-0380

UCSD is an Equal Opportunity-Affirmative Action Employer with a strong institutional commitment to the achievement of diversity among its faculty and staff.

POSITIONS OPEN

ASSISTANT OR ASSOCIATE PROFESSOR OF TECHNOLOGY ASSESSMENT

Stony Brook University's Department of Technology and Society, College of Engineering and Applied Sciences, seeks an Assistant or Associate Professor of technology assessment starting in September 2006. The Department's activities center on the design, management, and assessment of technological systems, and on the advancement of science and technology literacy. Required: Doctorate in science and technology studies or Doctorate in science or engineering, or closely related area, with strong background in interdisciplinary and policy studies. The candidate's background should have a strong emphasis on technology assessment and exhibit a broad range of interest in technology-society issues, substantial practical experience in carrying out technology assessments of current and/or emerging technologies, a demonstrated research program, a record of effective teaching, and interest in building new advanced degree programs. Must be able to evaluate the prospects and impacts of new technologies from an integrated multi-disciplinary perspective and design ways to use them for the greatest social, economic, environmental, and educational impacts. Applicants with backgrounds in environmental areas or practical experience in project management are encouraged. To apply, send a letter of application establishing qualifications, current curriculum vitae, detailed description of work experience and teaching philosophy, evidence of teaching effectiveness, a statement of research interests, and transcripts (official transcripts required at the time of an interview) to: **Rita Reagan Redko, Department of Technology and Society, College of Engineering and Applied Sciences, Stony Brook University, Stony Brook, NY 11794-3760.** We strongly recommend that candidates submit applications and accompanying materials, including names, addresses, and e-mail addresses of three references online at **website: http://www.stonybrook.edu/cjo.** *Affirmative Action/Equal Opportunity Employer.*

TENURE-TRACK FACULTY POSITION
The Biomolecular Research Center
Boise State University

The Biomolecular Research Center (BRC) at Boise State University seeks applicants for a tenure-track position in bioinformatics at the Assistant or Associate level. A doctoral degree in an appropriate field such as bioinformatics, biochemistry, computer science, computer engineering, mathematics, statistics or biology is required. Experience in algorithm development and an aptitude to work in cluster computer environments available at Boise State are required. Candidates must demonstrate a willingness to collaborate with multiple departments and develop an interdisciplinary program. This position requires a commitment to both research and education. The successful candidate will be expected to develop a strong, extramurally funded research program in proteomics, functional genomics or structural genomics and coordinate undergraduate and graduate courses in bioinformatics as well as develop new courses in area of expertise. For more information on the Center and participating departments, visit the Boise State hiring **website: http://hrs.boisestate.edu/joblistings** or the BRC **website: http://brc.boisestate.edu/.** Send applications including a cover letter, curriculum vitae, a statement of teaching interests and research plan, and contact information for three professional references in a single PDF to **e-mail: BarbaraJibben@boisestate.edu** with Bioinformatics Position in the subject line. Review of applications will remain open until position is filled. We are a rapidly growing research university in Idaho's capital city, which is highly ranked for livability, cultural offerings, and proximity to outdoor recreational activities. The location in a high-tech region with microelectronic industries and biomedical research centers provides a favorable environment for collaborative research. *Boise State University is an Equal Employment Opportunity/Affirmative Action Employer. Vets Preferences may be applicable.*

EVOLUTIONARY BIOLOGIST AT TENNESSEE

The Department of Ecology and Evolutionary Biology at the University of Tennessee, Knoxville seeks to fill a tenure-track position in evolutionary biology at the Assistant or Associate Professor level, to start August 1, 2006. Research in all areas will be considered, but especially attractive areas include macroevolution, phylogenetic theory, and broad-scale evolutionary processes in natural systems. Successful applicants will have demonstrated the ability to interact and collaborate broadly in ecology and evolution. Postdoctoral or faculty experience is preferred, and applicants will be expected to develop an externally funded and internationally recognized research program. Teaching will include undergraduate and graduate courses in the applicant's area. For more information visit **website: http://eeb.bio.utk.edu.**

The University welcomes and honors people of all races, genders, creeds, cultures, and sexual orientations, and values intellectual curiosity, pursuit of knowledge, and academic freedom and integrity.

Candidates should apply to:

Dr. Randall Small
Department of Ecology and Evolutionary Biology
569 Dabney Hall
University of Tennessee
Knoxville, TN 37996

Applicants should send curriculum vitae along with statements of research and teaching goals, and arrange for three reference letters to be submitted. Applications will be reviewed beginning January 6, 2006.

The University of Tennessee is an Equal Employment Opportunity/Affirmative Actionction/Title VI/TitleIX/Section 504/ADEA institution in the provision of its Education and Employment programs and services.

FACULTY POSITION
University of Wisconsin, Madison

Assistant Professor tenure-track position in Exercise Physiology available starting August 28, 2006. Earned doctorate is required and postdoctoral research experience is preferred. Area of research interest is open within the broad confines of biological aspects of exercise. Information about the Department is available at **website: http://www.education.wisc.edu/kinesiology/.** Applicants should send a letter of application, curriculum vitae, statement of research interests, copies of up to three published articles in refereed journals, and names, mailing addresses, e-mail addresses, and telephone numbers of three references to: **Professor Gary Diffee, University of Wisconsin, Department of Kinesiology, 2000 Observatory Dr., Madison, WI 53706. E-mail: diffee@education.wisc.edu.** (PVL 52124) To ensure full consideration, applications should be received by February 1, 2006. Unless confidentiality is requested in writing, information regarding the applicants must be released upon request. Finalists cannot be guaranteed confidentiality.

University of Wisconsin, Madison is an Equal Opportunity/Affirmative Action Employer. We promote excellence through diversity and encourage all qualified individuals to apply.

LOVE SCIENCE AND WANT A NON-TRADITIONAL BIOMEDICAL CAREER?

MEDICAL DIRECTOR/WRITER. CommonHealth, a leading medical communications group in northern New Jersey, is seeking a creative Physician or Scientist with an interest in physician education. Applicants must have MD, Ph.D., or Pharm. D. degree with research or patient care experience in oncology. Team player with well-developed writing and verbal communications skills. Strong ability to distill large volumes of data into readily understandable clinical information. Formats include journal articles, abstracts, posters, slides for presentations, proposals. Salary commensurate with experience. Send resume to **e-mail: srushevics@commonhealth.com.** Include salary requirements.

FACULTY POSITION
Physical Biochemistry

The Department of Chemistry and Biochemistry at California State University, Los Angeles is seeking applications to fill a tenure-track Assistant Professor position to begin September 2006. We seek an individual with instrument-intensive research interests in the area of analytical biochemistry or physical biochemistry, broadly defined. The successful applicant will have a Ph.D. degree in biochemistry, chemistry, or other molecular life science and a productive postdoctoral research experience with the potential to establish an extramurally funded research program that involves undergraduate and graduate students in collaborative research. The candidate will contribute to the biochemistry and other teaching needs of the Department. An attractive startup package including laboratory space, access to an instrumental core facility, and a significant reduction in teaching load for the first four years will be provided.

Please send curriculum vitae, description of research interests, and statement of teaching philosophy, and have three reference letters sent to: **Dr. Wayne Tikkanen, Department of Chemistry and Biochemistry, 5151 State University Drive, California State University, Los Angeles, CA 90032-8202.** Review of completed applications will begin January 16, 2006.

Equal Opportunity/Title IX/ADA Employer. Qualified women and minorities are encouraged to apply.

MOLECULAR NEUROBIOLOGIST
University of Wisconsin

Applications are invited for a junior tenure-track faculty position in the Department of Neurology at the University of Wisconsin. The position is intended to develop new translational programs with an emphasis on molecular neurobiology related to disease pathogenesis. Applicants should have a Ph.D. with appropriate training in molecular neurobiology. Applicants will be expected to develop an independent research program, pursue and obtain extramural support from the program and collaborate and interact with clinicians and scientist faculty. Applicants will also be expected to participate in Department teaching activities at the undergraduate, medical and graduate student and postdoctoral levels.

Salary and startup package will be commensurate with experience. Please send curriculum vitae, summary of research plan, and the names of at least three references to:

Thomas Sutula, M.D., Ph.D., Chair
Department of Neurology
University of Wisconsin
600 Highland Avenue
Room H6/574-5132 CSC
Madison, WI 53792-5132

PHARMACOLOGIST (CHAIR)

The American University of the Caribbean (AUC), a 25-year-old accredited medical school, with over 3,000 graduate physicians is continuing its search for the Chair of pharmacology (Ph.D. and/or M.D). Rank is commensurate with experience.

We seek an individual with experience and expertise, who both enjoys and is dedicated to teaching. The course in medical pharmacology will be team taught. Individuals familiar with United States medical education and evaluation systems are encouraged to apply. All lectures are in English, with PowerPoint formats and increasing use of e-learning modalities. An additional position may be recruited by the Chair. Applied research labs are being constructed.

AUC (**website: http://www.aucmed.edu**) is in a new, up-to-date facility on the delightful island of St. Maarten in the Netherlands, Antilles, some three hours by air from Miami.

Interested parties should send their curriculum vitae, and the names of three references with coordinates, via e-mail to: **Chair of the Search Committee,** at **e-mail: <buzs@aucmed.edu>.**

Lecturer with Potential for Security of Employment
University of California, San Diego
Division of Biological Sciences
http://biology.ucsd.edu/

The Division of Biological Sciences at the University of California, San Diego seeks outstanding applicants for an opening as Lecturer with Potential for Security of Employment or Lecturer with Security of Employment in Physiology and Embryology. All interested parties are encouraged to apply, including minorities and women.

The Lecturer will teach lecture and laboratory courses relevant to each area of study, (including Mammalian Physiology, Comparative Physiology, Embryology Laboratory) and be responsible for curriculum development including new laboratory offerings and participation in efforts to secure extramural funding for educational program development. In addition the successful candidates will be responsible for training of new laboratory Teaching Assistants and provide service to the University by participating in committees, recruitment and outreach efforts.

A Ph.D. in a relevant field of science is required. Applicants must have a strong record of excellence and innovation in teaching, along with strong interpersonal, writing and computer skills. The position will be a nine-month appointment. Salary and rank will be commensurate with background and experience and based on University of California pay scale. A Lecturer-PSOE position closely parallels that of an assistant professor on track for tenure.

Complete applications received by **January 15, 2006** will be assured consideration. Applicants should send a curriculum vitae, publication list, synopsis of professional goals, and three letters of reference (forwarded separately) to:

Lecturer Search Committee
c/o Kathleen McPherson – Mail Code 0357 - B
University of California, San Diego
9500 Gilman Drive
La Jolla, CA 92093-0355

UCSD is an Equal Opportunity-Affirmative Action Employer with a strong institutional commitment to the achievement of diversity among its faculty and staff.

10YR ANNIVERSARY

جامعة كارنيجي ميلون قطر
Carnegie Mellon QATAR CAMPUS
مؤسسة قطر
Qatar Foundation

Human-Computer Interaction Visiting Faculty Position in the School of Computer Science

Carnegie Mellon University established a branch campus in Qatar in the fall of 2004. We are offering a BS degree in Computer Science to an international student body. The university invites applications for a visiting faculty position to begin as early as January 2006.

We are seeking a faculty member in the area of Learning Science and Technology with research experience ideally in designing, implementing, deploying, and evaluating educational technology in school or college settings. An ability to teach courses in human-computer interaction, artificial intelligence, cognitive psychology, or related areas is also desired. The position will involve research in collaboration with the Pittsburgh Science of Learning Center and faculty at the Human-Computer Interaction Institute at Carnegie Mellon in Pittsburgh. The position offers competitive salaries, overseas assignments, travel and housing allowances and other benefits packages, as well as attractive research support.

Interested candidates should send their resume, statement of teaching interest and research, and names of three references to: **Faculty Hiring Committee, c/o Ruth Gaus, Qatar Office SMC 1070, 5032 Forbes Avenue, Pittsburgh, PA 15289; Ruth.Gaus@cs.cmu.edu; Fax 412-253-0924.**

- For more information on the Pittsburgh Science of Learning Center, see **http://learnlab.org**.
- For more information on the Human-Computer Interaction Institute, see **http://www.hcii.cs.cmu.edu**.
- For more information on the BS in CS program, see **http://www.csd.cs.cmu.edu/education/bscs/index.html**.
- For more information on the Carnegie Mellon Qatar Campus, see **http://www.qatar.cmu.edu/.**
- Information on Qatar is available at: **http://www.experienceqatar.com/**.

NICHOLAS SCHOOL OF THE ENVIRONMENT AND EARTH SCIENCES
DUKE UNIVERSITY

Director, Duke University Marine Laboratory

The Nicholas School of the Environment and Earth Sciences at Duke University seeks a Director for its Marine Laboratory in Beaufort, North Carolina. The successful candidate will also serve as Chair of the Division of Coastal Systems Science and Policy within the Nicholas School. We seek a candidate with expertise in the broad fields of ocean or coastal science or policy. The position will be filled at the rank of full professor, and will be resident at the Laboratory in Beaufort. We anticipate filling up to six faculty positions at the Laboratory during the next few years; thus, we seek an individual who can lead a mid-size teaching and research field station to a leading role in marine science and conservation in the next decade. The director will also play an instrumental role in enhancing undergraduate enrollment at the Laboratory and maintaining the excellence of the current professional masters and doctoral programs. The candidate should have familiarity with the operations of a marine facility and demonstrated experience in managing a facility or program.

The Marine Laboratory was founded in 1938 and has a distinguished reputation in marine science education, research and public involvement. There are currently 12 faculty and research scientists in residence. Further information may be found at: **http://www.nicholas.duke.edu/marinelab**.

Candidates should submit a cover letter highlighting relevant areas of experience, a curriculum vitae and three names of individuals familiar with the candidate's qualifications. Confidentiality will be maintained. Please send nominations, application materials and requests for information to: **Professor Joseph Ramus, Chair, Director Search Committee, Duke University Marine Laboratory, 135 Duke Marine Lab Road, Beaufort, NC, 28516-9721, USA. Phone: 252/504-7617. Fax: 252/504-7648. E-mail: jramus@duke.edu**. Review of applications will begin **February 1, 2006**, but we will continue to accept applications until the position is filled. The position is available as early as 30 June 2006.

Duke University is an Equal Opportunity, Affirmative Action Employer.

JOHNS HOPKINS
SINGAPORE
DIVISION OF BIOMEDICAL SCIENCES

The **Johns Hopkins University School of Medicine (JHUSOM**), Baltimore, MD, is initiating a search for a faculty position at the Assistant Professor in Bioengineering to join the Division of Biomedical Sciences, Johns Hopkins in Singapore (DJHS), an academic division of JHUSOM located in Singapore. Applications are invited from individuals with a biomedical engineering or biomaterials background and whose research interests are at the interface of tissue engineering and stem cell technology. The research is expected to complement the strong interest in stem cell biology of the Division. This will be a tenure-track position with appointments to JHUSOM and the Division.

Candidates should have PhD and/or MD degrees and a strong track record of research appropriate for appointment in the JHUSOM, and indicative of a high potential for creative scholarship. Generous salaries, benefits, and start up packages are available with funding for research programs for up to 3 years. Applicants should post, fax or e-mail their letter of inquiry and curriculum vitae to:

Ian McNiece, PhD
Director, Division of Johns Hopkins in Singapore
Professor of Oncology
Johns Hopkins University School of Medicine
31 Biopolis Way, #02-01, The Nanos
Singapore 138669
Tel: (65) 6874 0197 **Fax**: (65) 6874 0177
Email: imcniec1@jhmi.edu
Website: www.jhs.jhmi.edu

POSITIONS OPEN

The Department of Neuroscience, Cell Biology and Physiology at Wright State University (WSU), Dayton, Ohio, invites applications for a tenure-track faculty position at the **ASSISTANT OR ASSOCIATE PROFESSOR** level. The successful candidate will have research interest in neuroscience, with preference given to candidates with interest in autonomic regulation (especially in brainstem/peripheral receptor systems), and expertise with isolated cell/tissue preparations and/or anesthetized animals using electrophysiology, immunohistochemistry, and/or molecular biological tools. Candidates are expected to teach neuroscience in graduate and medical school courses. Requirements for the position include: a Ph.D. degree or equivalent doctorate, an excellent record of research accomplishments, ability to direct innovative independent research, competitive funding potential, and a strong commitment to high quality teaching. Applicants for the assistant rank must have at least two years of postdoctoral training and a record of publications demonstrating excellence in research and potential for obtaining extramural grant funding. Applicants for the associate rank must have at least four years of experience as an assistant professor and a record of publications and grants demonstrating a sustained quality research program with a national reputation for excellence and supervision of graduate students. Interested applicants should submit a curriculum vitae, statement of research and teaching interests, up to three representative reprints and/or preprints, and at the names of at least three references to: **Dr. Robert Putnam, Chair NCBP Faculty Search Committee, Department of Neuroscience, Cell Biology & Physiology, 235C Biological Sciences Building, Wright State University, 3640 Colonel Glenn Highway, Dayton, OH 45435** or **e-mail: ncbp@wright.edu.** *WSU is an Affirmative Action/Equal Opportunity Employer.*

FACULTY POSITION
Molecular Biophysics
Johns Hopkins University
School of Medicine

The Department of Biophysics and Biophysical Chemistry (**website: http://biophysics.med.jhmi.edu**) seeks outstanding candidates for the position of Assistant Professor. Applications are sought in all areas of molecular biophysics and biophysical chemistry, including structural biology. Priority will be given to applications received by February 1, 2006. Please submit curriculum vitae, a summary of current and proposed research, and arrange to have three letters of recommendation sent to:

Search Committee
Department of Biophysics
and Biophysical Chemistry
Johns Hopkins University
School of Medicine
WBSB 713
725 North Wolfe Street
Baltimore, MD 21205-2185
Fax: 410-502-6910
E-mail: biophysjob@bs.jhmi.edu

The Johns Hopkins University is an Equal Opportunity Employer.

RESEARCH ASSOCIATE POSITIONS are available immediately in a highly productive laboratory at University of Pittsburgh Cancer Institute to study signaling mechanisms that mediate glioma cell invasion and breast cancer metastasis. See **website: http://path.upmc.edu/people/faculty/sycheng.html** for more details of the laboratory's research interests and recent publications. Candidates who have a Ph.D. degree with strong publication records and expertise in molecular biology, signaling, cancer biology/histology and mouse models are desirable. Please send a short description of research experience and interests, curriculum vitae, and the names of three references to: **Shi-Yuan Cheng, Ph.D., University of Pittsburgh Cancer Institute, 5117 Centre Avenue, Pittsburgh, PA 15213, U.S.A. E-mail: chengshiyuan2005@yahoo.com.**

POSITIONS OPEN

POSTDOCTORAL AND
JUNIOR FACULTY POSITIONS
Ion Channel and Calcium Signaling Unit
Boston University
School of Medicine

Electrophysiologists, biochemists, molecular biologists and experts in high resolution imaging are encouraged to apply for positions ranging from Postdoctoral Fellow to Research Assistant Professor that are immediately available in the expanding Ion Channel and Calcium Signaling Unit at Boston University School of Medicine (BUSM). We are looking for dynamic and enthusiastic researchers to work on the novel mechanisms of ion channel regulation and calcium signaling, and their application to the cell physiology and disease. Candidates should have established expertise in one or more of the following: patch-clamp, high resolution imaging, advanced molecular and biochemical techniques, genetic manipulations. Curriculum vitae and three references should be submitted to:

Victoria M. Bolotina, Ph.D.
Director, Ion Channel and Calcium
Signaling Unit
Department of Medicine
Boston University
School of Medicine
650 Albany Street, X-704
Boston MA 02118 U.S.A.
E-mail: bolotina@bu.edu.

Boston University offers competitive salary and benefits and is an Equal Opportunity Employer.

ASSISTANT PROFESSOR
Department of Biological Sciences
Auburn University

Assistant Professor, DEVELOPMENTAL GENETICIST. The Biological Sciences Department of Auburn University and the Auburn University Peaks of Excellence Program in Cellular and Molecular Biosciences invites applications for a tenure-track position in developmental genetics. Candidates will be expected to possess expertise in functional genomics as broadly defined. Duties include teaching at the undergraduate and graduate levels and developing a vigorous, extramurally funded research program. A Ph.D. and minimum of two years of postdoctoral research are required. The candidate selected for this position, which will begin in August 2006, must meet eligibility requirements to work in the United States on date appointment is scheduled to begin and must be able to communicate effectively in English.

Applicants should submit curriculum vitae, statements of research interests and teaching philosophy, three representative reprints, and three letters of reference to: **Developmental Geneticist Search Committee Chair, Department of Biological Sciences, 101 Life Science Building, Auburn University, Auburn, AL 36849.** Review of applications will begin on January 15, 2006, and continue until the position is filled.

For more detailed information see **websites: http://www.auburn.edu/academic/science_math/biology/** or **http://www.auburn.edu/cmb.**

Auburn University is an Affirmative Action/Equal Opportunity Employer. Minorities and women are encouraged to apply.

POSTDOCTORAL RESEARCH POSITION
New York Medical College

A Postdoctoral Position is available, program focused on spindle checkpoint related cell cycle regulation, Ph.D./M.D., with more than three years of oncology, cell biology, biochemistry and medicine background is encouraged to apply. Salary is commensurate with experience but competitive. Send curriculum vitae and three references to: **BSB Room A03, New York Medical College, Valhalla, NY 10595.**

POSITIONS OPEN

ECOLOGIST

The Environmental Science Institute (ESI) and Integrative Biology of the University of Texas at Austin seek to hire an Ecologist. Although we are primarily searching at the Assistant Professor level, especially well-qualified individuals at other ranks will also be considered. We seek applicants who integrate ecology with other natural and social sciences to address ecosystem and environmental processes. We are particularly interested in areas related to carbon cycling, the water cycle, and climate change. A Ph.D. is required, and a degree in biological sciences and postdoctoral experience are preferred.

This position represents one of several new faculty positions authorized over the next five years to further ESI's (**website: http://www.esi.utexas.edu**) mission of conducting outstanding interdisciplinary research and education in environmental science. The successful applicant will have a faculty position in the Section of Integrative Biology (**website: http://www.biosci.utexas.edu/ib**), which has an active and growing ecology faculty.

We strongly encourage applicants to submit material as a single PDF file (including a cover letter, curriculum vitae, a brief statement of research and teaching interests and reprints/preprints of three pertinent publications) to **e-mail: esijob@uts.cc.utexas.edu.** A minimum of three recommendation letters should be sent by the references either in PDF or Word format to the above e-mail address, or in hard copy to: **Ecology Search, Section of Integrative Biology, The University of Texas at Austin, 1 University Station C0930, Austin, Texas 78712-0254 U.S.A.** Review of applications will begin December 31, 2005. For more detailed information see **website: http://www.biosci.utexas.edu/jobs/.** *The University of Texas is an Equal Employment Opportunity/Affirmative Action Employer.*

BIOGERONTOLOGY
University of Michigan

The University of Michigan Geriatrics Center is seeking to fill one or more **TENURE-TRACK FACULTY POSITIONS** from scientists who wish to develop independent research programs focused on biological gerontology. Applicants will be expected to develop a research program that uses methods in modern cell biology, genetics, bioinformatics, or molecular analysis to solve important problems in the biology of aging and its impact on late life pathophysiology. Research programs that emphasize mammalian models will be of particular interest, but others will also be considered. Successful candidates will be housed in newly constructed Geriatrics Center space, and will receive a primary appointment in a basic science or clinical department as appropriate. Minimum qualifications are a Ph.D., M.D., or equivalent degree, several years of highly productive postdoctoral research, and a clear interest in problems relevant to biogerontology. Substantial startup funding will be available for each selected candidate.

Applicants should submit a curriculum vitae, a brief (one-to-two page) description of research interests, a synopsis of current and previous research support, and contact information for three to five referees, to: **Karen Earl, 5303 CCGCB Box 0940, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0940.**

The University of Michigan is an Equal Opportunity Employer committed to maintaining diversity in its hiring programs.

POSTDOCTORAL FELLOWS
Harvard University

The first eight Environmental Fellows at Harvard University will be outstanding scholars with a Doctorate in any field and a research interest in the environment. Each Fellow will work with a host faculty member in the host's laboratory or office. Excellent salary and benefits. Apply by January 15, 2006. Details at **website: http://www.environment.harvard.edu.**

Harvard is an Equal Opportunity/Affirmative Action Employer.

POSITIONS OPEN

ACADEMIC DEPARTMENT HEAD
Biological Sciences, Ferris State University

The College of Arts and Sciences invites applications for the position of Biology Department Head, effective hiring date July 1, 2006. Ideal candidates will manifest a strong commitment to collegial leadership and support for faculty engaged in quality undergraduate teaching and learning. Successful applicants should also demonstrate skills that are essential to other aspects of departmental management in the categories of planning, assessment, budgeting, curriculum development, program evaluation, accreditation, faculty recruitment and supervision, student recruitment, student engagement, and fostering a supportive environment for grant writing and fundraising.

Required qualifications: applicants must have a Ph.D. in one of the biological sciences and must have at least five years of undergraduate teaching experience in a biological discipline. Successful academic administrative experience, success with fostering a supportive environment for faculty, experience with assessment, and strong interpersonal, written, and oral communication skills are also required.

Preferred qualifications: applicants with advanced rank and advanced successful administrative experiences are preferred. Candidates who have experience working with diverse staff and student populations, departmental and college collaborations, budget management, and familiarity with interdisciplinary curricula will strengthen their applications.

Review of applications will begin January 9, 2006, and continue until the position is filled. Candidates are asked to submit a completed Ferris State University employment application, provide a cover letter and curriculum vitae, a statement addressing their teaching philosophy and their philosophy of educational leadership, contact information of at least three references, and copies of college transcripts to: **JOB CODE SCIENCE-4380, Laurie Daniels, College of Arts and Sciences 420 Oak Street, PRK-150, Big Rapids, MI 49307.** Final candidates will be required to submit three letters of recommendation and official transcripts. A Ferris State University employment application can be obtained at the Jobs/Employers link on the University web page at **website: http://www.ferris.edu.** *An Equal Opportunity/Affirmative Action Employer.*

PALEOBOTANY: ESTELLA B. LEOPOLD ENDOWED PROFESSORSHIP AND CURATOR OF PALEOBOTANY

The University of Washington is seeking applications for a tenure-track, endowed faculty position to serve as Academic Curator of Paleobotany at the Burke Museum and as a Faculty Member in either the Department of Biology or the Department of Earth and Space Sciences. Appointment is anticipated at the Assistant Professor rank. In exceptional circumstances, appointment at the Associate or Full Professor level may be considered for candidates who have demonstrated a commitment to mentoring underrepresented students. Ph.D. required by date of appointment.

Because the Burke Museum maintains major holdings of Cenozoic floras, preference will be given to candidates doing research on the Cenozoic, but those researching other eras will be considered. Candidates should have a record of cutting-edge research, curatorial expertise, guiding student research based on collections, and promoting general scholarly and community access to collections. The candidate will be expected to obtain external research funding and to participate in undergraduate and graduate teaching.

Send curriculum vitae, description of research and teaching interests, three letters of reference, and PDF reprints of three recent publications to: **Carolyn Zick** at **e-mail:czick@u.washington.edu.** Priority will be given to applications received before 15 January 2006.

The University of Washington is building a culturally diverse faculty and strongly encourages applications from women and minority candidates. The University of Washington is an Equal Opportunity/Affirmative Action Employer.

CHAIR, DEPARTMENT OF PHARMACEUTICAL SCIENCES
Doctor of Pharmacy Program
Northeastern Ohio Universities
College of Medicine

Applications are invited for the position of Chair, Department of Pharmaceutical Sciences for the planned Doctor of Pharmacy program at Northeastern Ohio Universities College of Medicine (NEOUCOM). The Chair will provide leadership for the Department of Pharmaceutical Sciences with a direct reporting line to the Dean. Applicants must have a strong commitment to interdisciplinary education. The new College presents unique opportunities for developing interprofessional education of future pharmacists and physicians and plans to enroll its first pharmacy class in fall 2007.

The College seeks a candidate with a track record of successful scholarship, teaching, and service. Previous administrative experience is preferred, but not required. The Department Chair will work with pharmacy leadership to develop an innovative Doctor of Pharmacy program in close collaboration with medicine colleagues, consortium universities and clinical sites. The successful candidate will hold a Pharm.D. degree and/or a Ph.D. in the pharmaceutical sciences. Candidates will be expected to have a background in pharmacy education and research with preference given to those who have experience developing innovative and interdisciplinary education. Excellent communication skills as well as a passion for pharmacy education are critical attributes.

For a complete position description, requirements, and information on how to apply for this position please go to **website: http://www.neoucom.edu/DEPTS/HRES/EMPLOY.HTML.**

The Department of Neuroscience, Cell Biology and Physiology at Wright State University (WSU), Dayton, Ohio, invites applications for a faculty position at the **ASSISTANT OR ASSOCIATE PROFESSOR** level. The successful candidate will have research interest in the function, structure, development, and/or modification of synapses and circuits in the spinal cord or motor systems. Preference will be given to candidates using genetic animal models to study the formation and maturation of synapses and synaptic circuits. Candidates are expected to teach neuroscience in graduate and medical school courses. Requirements for the position include: a Ph.D. degree, an excellent record of research accomplishments, ability to direct innovative independent research, competitive funding potential, and a strong commitment to high quality teaching. Applicants for the assistant rank must have at least two years of postdoctoral training and a record of publications demonstrating excellence in research and potential for obtaining extramural grant funding. Applicants for the associate rank must have a record of publications and grants demonstrating a sustained quality research program with a national reputation for excellence and supervision of graduate students. Interested applicants should submit curriculum vitae, statement of research and teaching interests, up to three representative reprints and/or preprints, and at least three references to: **Dr. Francisco Alvarez, Chair NCBP Faculty Search Committee, Department of Neuroscience, Cell Biology and Physiology, 235C Biological Sciences Building, Wright State University, 3640 Colonel Glenn Highway, Dayton, OH 45435** or **e-mail: ncbp@wright.edu.** *WSU is an Affirmative Action/Equal Opportunity Employer.*

THE COLLEGE OF WOOSTER

BIOLOGIST. Full-time fall semester position for 2006 with ability to teach introductory biology and two upper level courses in ecology, evolution and/or conservation biology at The College of Wooster in Wooster, Ohio. See description at **website: http://www.ohio5.org/faculty.htm.** Choose Biology to locate the description or call or e-mail: **Dr. Dean Fraga, Chair, Department of Biology at 330-263-2557. E-mail: dfraga@wooster.edu.** *The College of Wooster is an Affirmative Action/Equal Opportunity Employer.*

THE SARAH AND DANIEL HRDY VISITING FELLOWSHIP IN CONSERVATION BIOLOGY

The Department of Organismic and Evolutionary Biology invites both nominations and direct applications for the Hrdy Visiting Fellowship in Conservation Biology. The Hrdy Visiting Fellowship is available either at the senior faculty level for one semester or a full year at the junior (i.e., postdoctoral) level, for the academic year 2006-2007. Duties will include teaching one course and/or giving lectures in conservation biology, as well as research and collaboration with members of the Harvard community. Applicants should identify a faculty sponsor(s), with whom they will collaborate. Please send a cover letter with a statement of intent, curriculum vitae, representative publications and arrange to have three letters of reference sent to:

Committee for Hrdy Fellowship
in Conservation Biology
Department of Organismic and
Evolutionary Biology
26 Oxford Street
Cambridge, MA 02138

Review of applications will begin on February 15, 2006.

Harvard University is an Equal Opportunity Employer.

ASSISTANT PROFESSOR OF ENTOMOLOGY, Integrative Behavioral Ecology. Twelve-month, tenure-track position with 80 percent research and 20 percent teaching. Develop a strong, extramurally-funded research program in insect behavioral ecology, focusing on areas that integrate levels of biological organization such as functional genomics, behavioral physiology, chemical ecology, or environmental bioassessment. Teach three courses over a four semester cycle: undergraduate general entomology, undergraduate/graduate course in either invertebrate zoology, aquatic entomology, or in area of interest, and graduate course in the area of specialty. Ph.D. in entomology or related area with postdoctoral research experience. Detailed position announcement available at **website: http://www.entomology.ksu.edu.** Send letter of application, research and teaching interests/philosophy, detailed curriculum vitae, relevant publications, and arrange to have three letters of reference sent to: **Dr. David Margolies, Chair, Search Committee, Department of Entomology, Kansas State University, Manhattan, KS 66506-4004. Telephone: 785-532-6154. Fax: 785-532-6232. E-mail: dmargoli@ksu.edu.** Review of applications will begin February 1, 2006, and continue until suitable candidate is found. *Kansas State University is an Equal Opportunity/Affirmative Action Employer. Women and minorities are encouraged to apply.* Paid for by Kansas State University.

POSTDOCTORAL POSITION to investigate chromatin remodeling and transcription in Toxoplasma gondii, a protozoan parasite related to malaria that causes opportunistic infections in AIDS patients **(see website: http://www.sullivanlab.com).** Strong background in biochemistry and molecular biology required. Send curriculum vitae to **e-mail: wjsulliv@iupui.edu,** or to:

Bill Sullivan Jr., Ph.D.
Indiana University
School of Medicine
635 Barnhill Drive, M.S. A-525
Indianapolis, IN 46202-5120

POSTDOCTORAL ASSOCIATE POSITIONS
Institute of Marine and Coastal Sciences
Rutgers, The State University of New Jersey

One year appointments, renewable, in the areas of biological, chemical, geological, and physical oceanography. Please send resume, a statement of research interest, and the names of three references by January 15, 2006, to: **Dr. J. Frederick Grassle, Rutgers, The State University, Institute of Marine and Coastal Sciences, 71 Dudley Road, New Brunswick, New Jersey 08901-8521.** *Rutgers is an Equal Opportunity/Affirmative Action Employer.*

MICHIGAN STATE UNIVERSITY

Program Director for Environmental Stewardship in Animal Agriculture

This is a senior level position that will be filled at the rank of Professor or equivalent.

Qualifications: Ph.D. in an applicable discipline. The successful candidate must have a proven track record in research and outreach activities in the general area of environmental stewardship in animal agriculture. This experience may be in academia, government, and/or industry.

Responsibilities and expectations: Develop a collaborative multi-disciplinary research and extension program focused on enhancing environmental stewardship in Michigan's animal agriculture industry.

Provide leadership and programming in the following specific areas:

- Liaison with government and regulatory agencies
- Serve as a source of information and cooperative energy on environmental regulatory issues
- Represent Michigan Agricultural Experiment Station and Michigan State University Extension
- Interact with MSU research and extension faculty across campus
- Identify funding opportunities and facilitate submission of multi-disciplinary and/or multi-state research proposals.
- Disseminate information on the issues of environmental stewardship in animal agriculture.

Salary is commensurate with qualifications and experience. Application materials will be accepted until January 30, 2006, or until a suitable candidate is identified. Please submit a letter of application, curriculum vitae, and the names of three references to: **Dr. Karen Plaut, c/o Kathy Tatro, 1290 Anthony Hall, Michigan State University, East Lansing, Michigan 48824, 517-355-8417**. The application packet may also be emailed to **tatro@msu.edu**. For a complete position description, visit **http://www.ans.msu.edu/employment/**.

MSU IS AN AFFIRMATIVE ACTION, EQUAL OPPORTUNITY INSTITUTION.

Sensor Research & Development Corp. in Orono, ME

Senior Materials Chemist to join a team in synthesizing nano-size semiconductor metal oxide (SMO) powders and sensing films for selective detection of chemicals. Develop novel materials for new sensing applications and build upon existing methods. Duties include all aspects of synthesizing materials and reviewing sensor data for sensitivity and selectivity. Contribute to proposals/reports. Preferred:

- PhD in material science or equivalent with experience on nano-size SMO sensing materials
- 5 yrs post-grad experience synthesis of SMO materials
- Microemulsion Sol-Gel technology and surface reactions
- Experience working on high temperature adhesive layers and additives for strengthening coating mechanics and binding properties
- Effective verbal, writing, and presentation skills
- Experience with molecular imprinted polymers (MIP)

Physical Chemist to support and develop cutting edge, optical-based systems for both chemical and biological detection. Includes operating and maintaining a suite of state-of-the-art optical equipment (microscopes, lasers, filters, etc.) Responsible for building new optical detection technologies. Duties include (1) designing and implementing optical systems to support experiments, (2) designing and running experiments and interpreting results, (3) proposing new optical-based detection strategies for company growth, (4) summarizing data for technical reports, proposals, and presentations, and (5) creating work plans to execute projects driven by optical-based technologies. Prefer:

- PhD in physical chemistry or equivalent
- 5 yrs hands-on experience with optical systems and spectroscopy technology (raman, cavity ring-down, etc)
- Exposure to bio-detection via optical technologies
- Knowledge of reaction chemistry and solid interfaces
- Experience with analytical detection equipment

SRD offers a full benefit package. Please send resume and three references to: **techjobs@srdcorp.com**.

We are an Equal Opportunity and Affirmative Action Employer.

Beth Israel Deaconess Medical Center

A teaching hospital of Harvard Medical School

CANCER BIOLOGIST

The Department of Pathology at Beth Israel Deaconess Medical Center is seeking a full-time biomedical scientist at the Assistant Professor level in the area of cancer biology. The Medical Center is a tertiary care facility and a major teaching hospital of Harvard Medical School. The Department of Pathology is embarking on the most ambitious program of growth in its history and is actively expanding the strength and depth of both its clinical and research faculty. Ground has been broken for a new, state-of-the-art research building that will accommodate most of the research scientists within the Medical Center and all of the scientists within the Pathology Department.

We are seeking candidates of exceptional promise who have strong records of research creativity and productivity in basic or translational research in the field of cancer. Work may involve the use of model organisms to identify fundamental mechanisms of malignant transformation, tumor cell signal transduction, cancer genetics, tumor cell growth and apoptosis, metastasis and/or tumor angiogenesis. The work may also emphasize development and exploitation of new technologies and strategies in cancer diagnosis and treatment.

The successful candidate will receive a highly competitive start-up package, appointment to the faculty of Harvard Medical School and full membership in the Beth Israel Deaconess Cancer Biology Research Center. The Department of Pathology strongly encourages interactions among research and clinical faculty and provides opportunities to access an extraordinary human tumor resource through its Divisions of Anatomic Pathology and Laboratory Medicine. We also provide unparalleled opportunities for collaborative interactions among the basic and applied cancer biology research community at Harvard Medical School, its affiliated teaching hospitals, and Dana Farber Cancer Institute.

Applicants must hold a PhD and/or MD degree. Beth Israel Deaconess Medical Center is committed to increasing the representation of women and members of minority groups on its faculty, and we particularly encourage applications from such candidates.

Interested applicants should submit a curriculum vitae, a statement outlining existing and planned research activities and career goals, and the names of three professional references to:

Dr. Jack Lawler, Director, Division of Cancer Biology and Angiogenesis
Beth Israel Deaconess Medical Center
Research North, Room 270C, 99 Brookline Avenue, Boston, MA 02215

FACULTY POSITIONS in TRANSLATIONAL RESEARCH

The Nevada Cancer Institute is seeking tenure-track investigators at the **ASSISTANT, ASSOCIATE, and FULL MEMBER** levels to join the Drug Development Division of this newly established cancer research center. The positions offer outstanding scholarly and scientific resources in a collegial and collaborative clinical and research environment (website: **http://www.nevadacancerinstitute.org**).

Preference will be given to investigators using molecular and cellular approaches to identify novel drug targets for the development of new anti-cancer drugs. Candidates with research interests in any of the following areas are strongly encouraged to apply: mammalian cell cycle and checkpoint control, in-vivo and molecular imaging, apoptosis, and other emerging areas of cancer research.

Candidates will be judged on their potential to establish and maintain an externally funded research program that investigates current scientific issues in the area of drug development, discovery of novel drug targets, mechanisms, monitoring and analysis at the chemical and biological level. The successful candidate will be expected to create a research and educational program in drug investigation that attracts resources from government funding agencies, private foundations, and private industry.

Applicants should have an MD and/or PhD or the equivalent. Interested applicants should submit an outline of current and future research interests, funding history, a CV and the names and addresses of three references to:

Giuseppe Pizzorno, Ph.D., Pharm.D.
Vice President of Research Operations and Head of Drug Development
c/o John Gilani
Nevada Cancer Institute
10000 W. Charleston # 140
Las Vegas, NV 89135
or email to: **jgilani@nvcancer.org**

Review of applications will commence immediately and continue until positions are filled.

POSITIONS OPEN

The United States Department of Agriculture (USDA), Agricultural Research Service (ARS), Mosquito and Fly Research Unit in Gainesville, Florida, is seeking a **POSTDOCTORAL RESEARCH ASSOCIATE, (Research Entomologist/Research Toxicologist/Research Molecular Biologist)** for a two year appointment. Ph.D. is required. Salary is commensurate with experience ($50,541 to $78,745 per annum) plus benefits. Citizenship restrictions apply. The incumbent will employ various bioassays, synergism studies, electrophysiology, chromatography, and other biochemical analysis to elucidate the mode of action of insecticidal compounds and to assist in the identification of novel and specific targets for toxicological screening. Knowledge of insect molecular biology, functional genomics, biochemistry and/or medical entomology is required. Refer to **website: http://www.ars.usda.gov/careers** for further information on Postdoctoral Research Associate jobs, for complete application instructions, and the full text announcement (RA-05-068L). Send application materials and references to: **Dr. James Becnel, USDA/Agricultural Research Service, CMAVE, Mosquito and Fly Research, 1600-1700 SW 23rd Drive, Gainesville, Florida, 32608** or **e-mail: jbecnel@gainesville.usda.ufl.edu.** *USDA/ARS is an Equal Opportunity Provider and Employer.*

POSTDOCTORAL POSITIONS
Neuroendocrinology/Alcohol Research

Two full-time Postdoctoral Associate positions for two to five calendar years are available immediately. Duties for these positions include research to determine the molecular mechanisms governing the circadian control of neuroendocrine functions in normal and fetal alcohol exposed adult rats. Research experience in rodent surgeries, radioimmunoassays and immunocytochemistry and/or cell cultures, real-time polymerase chain reaction (RT-PCR), cloning, and transcriptional and gel-shift assays are essential. Good written and oral communication skills are required. Send curriculum vitae and three letters of reference to: **Dipak K. Sarkar, Director, Endocrine Program, 84 Lipman Drive, Rutgers University, New Brunswick, NJ 08901,** or to **e-mail: sarkar@aesop.rutgers.edu.**

CONSERVATION ECOLOGIST. The Wilderness Society seeks an experienced Conservation Ecologist, with an ability to work in the nexus between public policy and science, to join our regional conservation team's efforts to protect California's wildlands. We seek an applied Ecologist who can synthesize and analyze existing scientific information, develop new information, and translate these ideas into a format that will influence federal land management decisions in California. For a complete job description see the career page at **website: http://www.wilderness.org.** To apply, please submit a cover letter explaining your qualifications for this position, along with a resume and writing sample. Include names, addresses, and telephone numbers of three references. Send to: **Ms. Geri Wardlow, Recruiting Consultant, 1615 M Street, Washington, D.C. 20036. Fax: 703-327-0415. E-mail: geriw@tws.org.**

POSTDOCTORAL POSITION available to study negative regulation of antigen presentation and to develop novel immunotherapy and vaccines against tumors. Experience in gene transfer and immunology, especially dendritic cell (DC) biology, mouse models, and Adv vector is preferred. Send curriculum vitae and three references to: **Dr. Xue F Huang, Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, TX 77030. E-mail: xhuang@bcm.tmc.edu.**

Baylor College of Medicine is an Equal Opportunity/Affirmative Action/Equal Access Employer.

POSTDOCTORAL POSITION
Conservation Biology and Policy
Woodrow Wilson
School of Public and International Affairs
Princeton University

We seek an innovative, enthusiastic individual ready to develop new, practical approaches to issues of systematic conservation planning and progress assessment, focusing on Florida. The successful candidate will work closely with **Professor David Wilcove** in collaboration with The Nature Conservancy. Candidate must demonstrate strong interest in conservation, familiarity with conservation planning literature, and strong collaborative and computational skills, including ability to analyze large spatial datasets. Experience with habitat modeling, geographic information system (GIS), programming, and/or reserve-design algorithms helpful. Applicants must have Ph.D. in ecology, conservation biology, or related field. Competitive salary, commensurate with experience, and excellent benefits offered. Review of applications begins January 9, 2005. Send application including curriculum vitae, statement of research interest, and names of three references to: **Geraldine Rhodes, Robertson Hall, Princeton University, Princeton, NJ 08544. E-mail: grhodes@princeton.edu.** *Princeton University is an Equal Opportunity/Affirmative Action Employer.*

POSTDOCTORAL FELLOWSHIP
Population Dynamics and Spatial Modeling
Center for Environmental Analysis, Centers for Research Excellence in Science and Technology

The Center for Environmental Analysis, California State University at Los Angeles **(website: http//:cea-crest.calstatela.edu)** seeks a postdoctoral researcher with expertise in modeling population dynamics. Experience in ODE modeling, spatially explicit modeling, geographic information system (GIS), spatial statistics, or experimental design preferred. Responsibilities include developing and evaluating spatially explicit models of marine population dynamics, as part of collaboration between marine scientists of the Center for Environmental Analysis, Centers for Research Excellence in Science and Technology (CEA-CREST) and theorists of the Control and Dynamical Systems Division, California Institute of Technology. Responsibilities include coordinating and assisting graduate and undergraduate students matriculated in modeling courses at the California Institute of Technology. Salary is $35,000 to $38,000 per year for two years. Application letter, curriculum vitae, and three letters of recommendation should be sent to: **Dr. Robert Desharnais, Department of Biology, California State University at Los Angeles, CA 90032. E-mail: rdeshar@calstatela.edu. Telephone: 323-343-2056.**

A **POSTDOCTORAL POSITION** in molecular biology/biochemistry is immediately available in **Dr. Xi Chen's** laboratory in the Department of Chemistry at the University of California, Davis. The position will focus on cloning, biochemical characterization, mutagenesis, and crystal structure studies of glycosyltransferases and other glycan biosynthetic enzymes. Candidates with background in molecular biology and/or biochemistry are encouraged to apply. Interested individuals should e-mail curriculum vitae and contact information of three references to **e-mail: chen@chem.ucdavis.edu.** Visit **website: http://chemgroups.ucdavis.edu/~chen/home.htm** for additional information.

POSTDOCTORAL POSITION is available immediately to investigate mechanisms of Candida albicans invasion of host cells during systemic and oropharyngeal disease. Research involves targeted gene disruption in C. albicans, identification of host cell and fungal receptors, signal transduction analysis, and assessment of virulence in murine models. Experience in molecular and cellular biology desired. Please submit curriculum vitae, summary of research experience, and three references to: **Dr. Scott G. Filler, Los Angeles Biomedical Research Institute, 1124 W. Carson Street, Torrance, CA 90502. E-mail: sfiller@ucla.edu.**

POSTDOCTORAL AND CLINICAL FELLOWSHIPS
at the
National Institutes of Health
U.S. Department of Health and Human Services

Website: http://www.training.nih.gov

NIH is dedicated to building a diverse community in its training and employment programs.

RESEARCH ASSOCIATE

The Pennington Biomedical Research Center (PBRC), a research facility of Louisiana State University (LSU) System is seeking to hire a Research Associate to work in the Animal Phenotyping Core of the newly funded Clinical Nutrition Research Unit. The successful applicant will join a team of researchers investigating nutritional programming, the metabolic, molecular and genomic mechanisms through which diet and nutrients alter physiological processes related to obesity and diabetes. Required qualifications: Master's or Ph.D. in biological sciences, biological engineering or a related discipline. Previous experience of working with laboratory animals would be advantageous. Salary will be commensurate with experience. Applications will be accepted until a suitable candidate is found. Please submit resume, including curriculum vitae, and the names of three references to:

Director of Human Resources
Ref: York – RA- 014873
Pennington Biomedical Research Center
6400 Perkins Road
Baton Rouge, LA 70808

Electronic mail should be sent to **e-mail: Jobs@pbrc.edu.**

LSU/PBRC is an Equal Opportunity/Equal Access Institution.

POSTDOCTORAL POSITIONS
Australian Research Council Centre of Excellence

The Australian Research Council (ARC) Centre of Excellence for Coral Reef Studies is an international research centre administered by James Cook University in partnership with the Australian Institute of Marine Science, The Australian National University, the Great Barrier Reef Marine Park Authority, The University of Queensland and 23 other institutions and Industry Partners in nine countries.

The Centre will offer up to twelve two to three year postdoctoral positions in Australia for graduates with research interests in areas relevant to coral reefs including coastal history, social science, economics, mathematics, ecology, physiology, evolutionary and molecular biology or biogeography. Details at **website: http://www.jcu.edu.au/app/jobs/searchfacdiv.cfm.**

FELLOWSHIPS

THE HEISER PROGRAM FOR RESEARCH IN LEPROSY AND TUBERCULOSIS

Beginning **POSTDOCTORAL RESEARCH FELLOWSHIPS** in leprosy and tuberculosis available at stipend levels between $30,000 and $35,000 (plus allowances), and **RESEARCH GRANTS** in leprosy only in amounts up to $35,000.

Applicants should have M.D., Ph.D., or equivalent degree. Application deadline March 1, 2006, for awards to be activated August through December, 2006. For information and forms see **website: http://www.NYCommunitytrust.org.** Click on Grantmaking and select Special Programs. For questions or problems with application forms, **e-mail: lm@nyct-cfi.org.**

MEETINGS

AWARDS

THE 2006 LOUISA GROSS HORWITZ PRIZE FOR BIOLOGY OR BIOCHEMISTRY

COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK

The Louisa Gross Horwitz Prize was established under the will of the late S. Gross Horwitz through a bequest to Columbia University and is named to honor the donor's mother. Louisa Gross Horwitz was the daughter of Dr. Samuel David Gross (1805–1889), a prominent surgeon of Philadelphia and author of the outstanding *Systems of Surgery*, who served as president of the American Medical Association.

Each year since its inception in 1967, the Louisa Gross Horwitz Prize has been awarded by Columbia University for outstanding basic research in the fields of biology or biochemistry. The purpose of this award is to honor a scientific investigator, or group of investigators, whose contributions to knowledge in either of these fields is deemed worthy of special recognition.

The Prize consists of an honorarium and a citation which are awarded at a special presentation event. Unless otherwise recommended by the Prize Committee, the Prize is awarded annually. Dr. Ada Yonah of the Weizmann Institute of Science, Rehovot, Israel, was the 2005 awardee.

QUALIFICATIONS FOR THE AWARD

The Prize Committee recognizes no geographical limitations. The prize may be awarded to an individual or a group. When the prize is awarded to a group, the honorarium will be divided among the recipients, and each member will receive a citation. Preference will be given to work done in the recent past.

Prospective recipients should be nominated electronically at: http://cumc.columbia.edu/horwitz/

Electronic nominations should include:

1. A summary, preferably less than 500 words, of the research on which this nomination is based.
2. A summary, preferably less than 500 words, of the significance of this research in the fields of biology or biochemistry.
3. A brief biographical sketch of the nominee, including positions held and awards received by the nominee.
4. A listing of up to ten of the nominee's most significant publications relating to the research noted under item 1.
5. A copy of the nominee's curriculum vitae.

Nominations must be submitted no later than **January 21, 2006.**

Announcement of an NIH Roadmap Research Funding Opportunity

ASSAY DEVELOPMENT FOR HIGH THROUGHPUT SCREENING

Request for applications RM-06-004

This RFA is one component of the NIH Roadmap Molecular Libraries and Imaging Initiative (**http://nihroadmap.nih.gov/molecularlibraries/**). Its goal is to initiate a stream of scientifically novel and technologically robust assays that can be miniaturized, automated, and used for screening small molecules. Investigators are asked to state a biological question that can be addressed through the use of a pharmacological small molecule probe, to further define the properties that should be encompassed in the probe design, and to develop assays that can be incorporated into a screening plan aimed at identifying small molecules with essential probe attributes.

Projects to develop promising assay protocols for novel molecular targets will be supported by a 1-year R21 ($125,000 available in direct costs). Projects to transition established assays to a *high throughput screening* format, and further define a screening project plan, will be supported by an R03 mechanism for 1 year ($50,000 available in direct costs). Emphasis will be placed on screening targets for which an inadequate array of selective and potent small molecule modulators are available to the public.

The RFA is intended to promote the development of automated screening projects that will be eligible for submission to the newly established Molecular Libraries Screening Network via the PAR-05-147 announcement listed at the link above. The overall goal of the Molecular Libraries and Imaging Initiative is to create a public database of biological information about small molecule chemical structures (see PubChem: **http://pubchem.ncbi.nlm.nih.gov**), which will further seed the development of small molecule pharmacological tools for biological research.

It is anticipated that 40-50 projects will be funded (for $6 million) in response to two announcement dates in 2006, with further announcements planned for succeeding years. Investigators should submit a letter of intent by **December 29, 2005** for the next submission date of January 12, 2006. Additional information about the announcement can be obtained at the following website: **http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-06-004.html**. The Program Director, **Mark Scheideler, Ph.D.**, can be contacted by email at: **scheidelerm@ninds.nih.gov**.

SYMPOSIA

A National Symposium:

Seeking Ponce's Dream

The Promise of Predictive Health

December 19-20, 2005

Emory Conference Center,
Atlanta, Georgia

Speakers include:
Lee Hood, PhD
Ralph Snyderman, MD
Tom Wolfe

Sponsored by:

EMORY UNIVERSITY

Georgia Institute of Technology

The Emory/Georgia Tech Predictive Health Institute

For more information visit the website or contact Lynn Cuningham at (404) 727-6543 or lynn.cunningham@emory.edu.

www.whsc.emory.edu/public_events.cfm
Then select "Predictive Health Symposium: Seeking Ponce's Dream" at the bottom of the page.

DORIS DUKE
CHARITABLE FOUNDATION

Doris Duke Charitable Foundation Announces Two Clinical Research Award Competitions

Clinical Scientist Development Awards

Fostering Careers in Research

CALL FOR PRE-PROPOSALS

This program supports junior-level physician-scientists conducting clinical research in cardiovascular diseases, cancer, AIDS and other infectious diseases, and sickle cell anemia and other blood disorders.

Up to 12 awards of $135,000/year for three years will be made to investigators at the instructor or assistant professor level.

Formal institutional nominations are not required. Interested physician-scientists meeting the eligibility requirements should submit a brief pre-proposal. Full details and instructions are available at: www.ddcf.org/mrp-csda.

Application Deadlines

Pre-Proposals Due: January 31, 2006
Invited Proposals Due: April 18, 2006

Distinguished Clinical Scientist Awards

Recognizing Excellence in "Bench to Bedside" Research

CALL FOR NOMINATIONS

This program supports mid-career physician-scientists conducting "bench-to-bedside" (translational) research in any area of clinical investigation.

Up to five awards of $1.5 million for five years will be made to investigators at the associate professor level or higher who have an established translational clinical research program and an outstanding mentoring record.

Academic medical centers and other non-profit research institutions in the U.S. can nominate up to two candidates. Full details and instructions are available at: www.ddcf.org/mrp-dcsa.

Application Deadlines

Nomination Packages Due: February 14, 2006
Invited Proposals Due: June 6, 2006

DORIS DUKE
CHARITABLE FOUNDATION

Congratulations to the Following New Doris Duke Awardees

2005 Clinical Interfaces Award Program

Team Awards at the Interface of the Clinical and Basic Sciences

"Clinical application of molecular imaging to oncology"

Michael V. Seiden, MD, PhD, Arlan Fuller, MD, Jeffrey Supko, PhD, Debra Bell, MD and Mukesh G. Harisinghani, MD / Massachusetts General Hospital

"A mitochondrial basis for metabolic syndrome"

Douglas Wallace, PhD, J. Jay Gargus, MD, PhD, F. Sherwood Rowland, PhD, Donald R. Blake, PhD, and Bruce J. Tromberg, PhD / University of California, Irvine

"Development of the first test for common cancer risk in the general population"

Andrew P. Feinberg, MD, MPH, Marcia Cruz-Correa, MD, PhD, Francis M. Giardiello, MD, Elizabeth A. Platz, ScD, MPH, Christi Iacobuzio-Donahue, MD, PhD, MPH, Holly Taylor, PhD, Benjamin Wilfond, MD, and Hengmi Cui, PhD / Johns Hopkins University School of Medicine

2005 Clinical Scientist Development Award Program

Michelle Asha Albert, MD, MPH, Brigham and Women's Hospital/Harvard Medical School, *"Black women's health study and cardiovascular risk"*

Corey Casper, MD, MPH, University of Washington School of Medicine, *"HHV-8 replication and progression to malignancy in Africa"*

Sekar Kathiresan, MD, Broad Institute of MIT and Harvard, *"Osteoprotegerin pathway biomarkers, genes, and CVD"*

Jeffrey R. Keefer, MD, PhD, Johns Hopkins University School of Medicine, *"Pharmacological modulation of fetal hemoglobin"*

Allison A. King, MD, MPH, Washington University School of Medicine, *"Cognition in children with sickle cell anemia"*

Matthew E. Mealiffe, MD, University of Washington School of Medicine, *"K7: A gene for Hodgkin's lymphoma predisposition"*

William Pao, MD, PhD, Memorial Sloan-Kettering Cancer Center, *"Acquired resistance to targeted therapy in lung cancer"*

Pavan R. Reddy, MD, University of Michigan, *"Immuno-modulation by histone deacetylase inhibitors"*

Neil Shah, MD, PhD, UCSF School of Medicine, *"Perfecting targeted therapy for human malignancies"*

John J. Strouse, MD, Johns Hopkins University School of Medicine, *"Cerebral blood flow in sickle cell disease"*

Rochelle P. Walensky, MD, MPH, Massachusetts General Hospital/Harvard Medical School, *"The impact and value of routine HIV testing in South Africa"*

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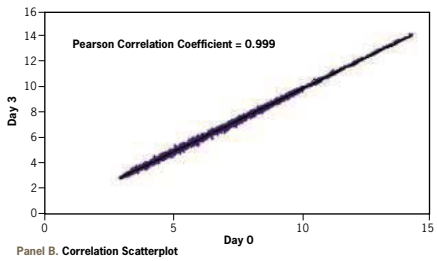
	Yield	28S/18S rRNA Ratio	RIN
Day 0	17.0 ± 1.7	1.3 ± 0.06	8.4 ± 0.4
Day 3	19.7 ± 1.5	1.2 ± 0.06	8.0 ± 0.2

Panel A. **RNA Metrics**



Panel B. **Correlation Scatterplot**

	Avg. % Present calls	Avg. GAPDH (3'/5')	Avg. Actin (3'/5')
Day 0	53.2	1.15	0.95
Day 3	51.0	1.16	0.97

Panel C. **Microarray Metrics**

Maintain a Stable Expression Profile after Storage of WBCs on LeukoLOCK™ Filters
RNA was prepared using the LeukoLOCK Total RNA Isolation System from leukocytes processed immediately or stored on the LeukoLOCK Filter for 3 days at room temperature. **(A)** RNA yield and quality were determined using a NanoDrop® Spectrophotometer and Agilent® 2100 bioanalyzer expert software. **(B)** Total RNA (1 µg, no globin reduction treatment) was amplified using Ambion's MessageAmp™ II-96 aRNA Amplification Kit. Fragmented aRNA was then hybridized to Human Focus Arrays (Affymetrix®) and scanned with a GeneChip® Scanner 3000. Data were captured and analyzed on GeneChip Operating Software (Affymetrix). A correlation plot from the normalized data is shown for the average array signal intensities for day 0 vs. day 3 biological replicates. **(C)** Percent Present calls and GAPDH and β-actin 3' to 5' ratios were also assessed.

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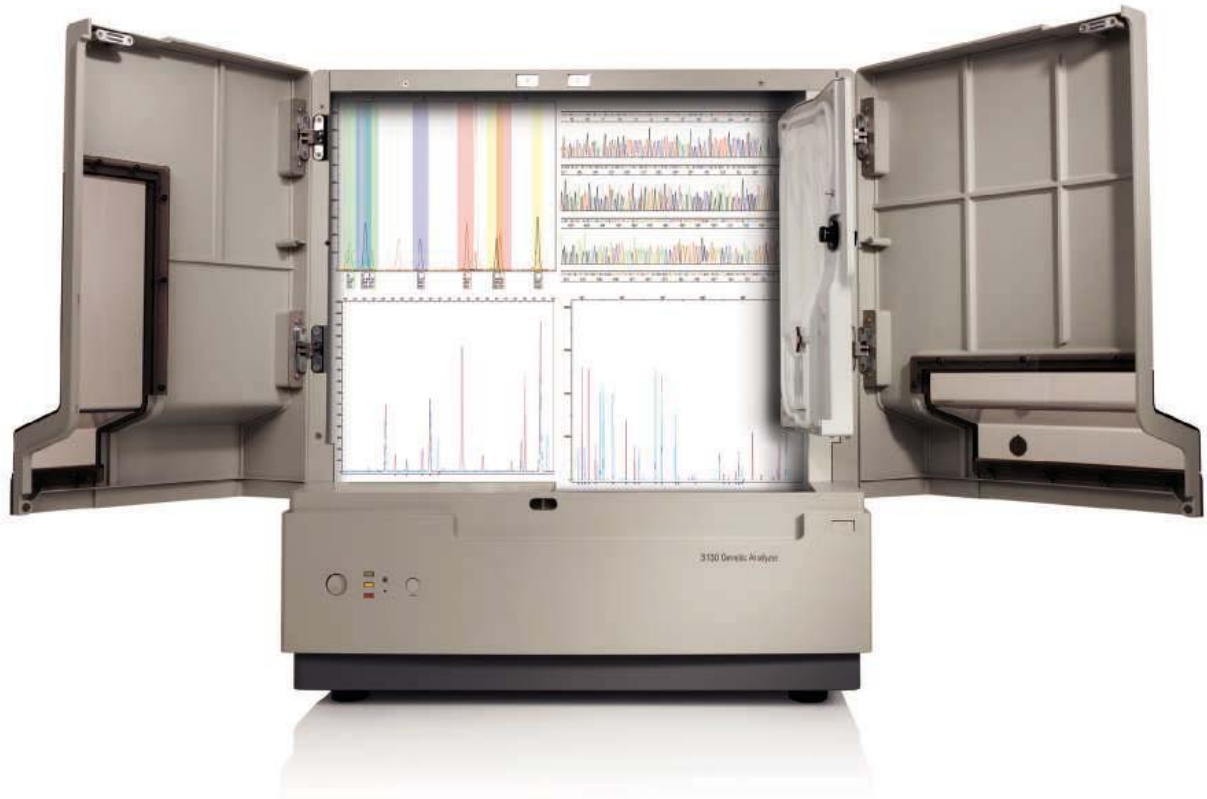

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